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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,410	05/29/2007	Deborah Hurst	PP020110.0005/59516-313	5534

7590 04/15/2009

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
04/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,410	HURST ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 33-39* is/are pending in the application.

4a) Of the above claim(s) *16-21 and 33-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/19/07*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group II, claims 1-15, a method for treating chronic lymphocytic leukemia, using an anti-CD52 antibody and a variant of IL-2 in the reply filed on 01/27/09 is acknowledged.

The traversal is on the ground(s) as follows:

As noted by the Examiner, the present application is a national phase filing of PCT~S2004/017921 filed under 35 U.S.C. 371. Accordingly, questions of unity must be resolved using the criteria of Rule 13 of the Patent Cooperation Treaty (PCT). As the Examiner has pointed out and as explained in 37 CFR 1.475(b)(2), when claims to different categories are present in the application, such as a product and a process of use of said product, the claims will be considered to have unity of invention.

Here, the claims of Group II, directed to a method of treating chronic lymphocytic leukemia using an anti-CD52 antibody and a variant of interleukin-2, and the claims of Group III, drawn to an anti-CD52 antibody and a variant of interleukin-2, should be examined together since they are directed to a product and a process of use of that product.

This is not found persuasive because of the following reasons:

Groups I-III of the claimed inventions do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as groups I-III do not relate to a single general inventive concept because they lack the same or corresponding special technical feature.

The technical feature of group I, an interleukin-2 or an anti-CD52 antibody is known in the art, as taught by Kay et al, 1988, Nouv Rev Fr Hematol, 30: 475-478, IDS of 04/19/07 or Regier et al, Feb 2004, Leukemia & Lymphoma, 45(2): 345-349, respectively. Thus the claimed invention lacks novelty and does not make a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

After review and reconsideration, claims 1-15,, a method for treating chronic lymphocytic leukemia using an anti-CD52 antibody and an interleukin-2 are rejoined with group II, claims 1-15, a method for treating chronic lymphocytic leukemia, using an anti-CD52 antibody and a variant of IL-2, in view that a method for treating chronic lymphocytic leukemia using an anti-CD52 antibody and an interleukin-2 is known in the art (see Kay et al, 1988, Nouv Rev Fr Hematol, 30: 475-478, IDS of 04/17/09 and Regier et al, Feb 2004, Leukemia & Lymphoma, 45(2): 345-349).

Claims 22-25 are withdrawn as drawn to non statutory subject matter with "use" claims. As such these claims are withdrawn from consideration.

Accordingly, claims 1-15are examined in the instant application.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite, because it is not clear what zig and p.g. are, which are not art recognizable dosage units used for the mutant interleukin Aldesleukin. In the specification, the weekly dose of aldesleukin is in the range of 1100ug to 2565 ug, which dosage provides at least 50% of the NK stimulatory activity of the total weekly dose of aldesleukin (p.7, first paragraph).

Claim Rejections - 35 USC § 112, First Paragraph, Scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for a method for treating chronic lymphocytic leukemia, using an anti-CD52 antibody and an interleukin-2 or a variant thereof, does not reasonably provide enablement for a method for treating chronic lymphocytic leukemia, using **a fragment** of an anti-CD52 antibody, Alemtuzumab, and an interleukin-2 or a variant thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

One would not know how to use the claimed method, because an immunologically active fragment of an anti-CD52 antibody does not necessarily bind to the CD52 antigen, in view that any peptide fragment would be immunologically active, i.e., producing an immune response.

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, <u>if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling</u>."

Given the above, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-2, 4-9, 11-13, are rejected under 35 U.S.C. 103(a) as being unpatentable over Regier et al, Feb 2004, Leukemia & Lymphoma, 45(2): 345-349), in view of Kay et al, 1988, Nouv Rev Fr Hematol, 30: 475-478, IDS of 04/17/09, and further in view of Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract only, and Dmoszynska et al, 1999, Leukemia & Lymphoma, 34(3-4): 335-340, IDS of 04/17/09.

Claims 1-2, 4-9, 11-13, are as follows:

1. (Original) A method of treating chronic lymphocytic leukemia in a human subject, said method comprising administering to said subject at least one cycle of concurrent therapy with an anti-CD52 antibody and an interleukin-2 (IL-2).

2. (Original) The method of claim 1, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or a variant thereof having at least 70% sequence identity to the amino acid sequence for human IL-2.

4. (Currently Amended) The method of claim 1, wherein said anti-CD52 antibody is an immunologically active anti-CD52 antibody.

5. (Original) The method of claim 4, wherein said anti-CD52 antibody is Alemtuzumab or fragment thereof.

6. (Original) A method of treating chronic lymphocytic leukemia in a human subject, said method comprising administering to said subject at least one cycle of concurrent therapy with an anti-CD52 antibody and an interleukin-2 (IL-2), wherein said cycle comprises administering a therapeutically effective dose of an anti- CD52 antibody according to a weekly,

twice-weekly, or thrice-weekly dosing schedule in combination with administration of a constant IL-2 dosing regimen, said constant IL-2 dosing regimen comprising administering a total weekly dose of an IL-2 to said subject.

7. (Original) The method of claim 6, wherein a first dose of an IL-2 is administered to said subject concurrently with a first dose of an anti-CD52 antibody.

8. (Original) The method of claim 7, wherein a first dose of an IL-2 is administered to said subject one week after a first dose of an anti-CD52 antibody is administered to said subject.

9. (Currently Amended) The method of claim 6, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or a variant thereof having at least 70% sequence identity to the amino acid sequence for human IL-2.

11. (Original) The method of claim 6, wherein said anti-CD52 antibody is an immunologically active anti-CD52 antibody.

12. (Original) The method of claim 11, wherein said anti-CD52 antibody is Alemtuzumab or fragment thereof.

13. (Original) The method of claim 6, wherein one or more subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody is initiated about 1 month to about 6 months following completion of a first cycle or completion of any subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody.

Rieger et al teach treating chronic lymphocytic leukemia (CLL) using Alemtuzumab, which is a humanized anti-CD52 antibody (abstract, and p.345). Rieger et al suggests flexible time intervals for the anti-CD52 antibody injection, depending on leukocytes counts, because

application three times a week at a dose of 30mg each for 12 weeks causes hematotoxicity in many patients (abstract, p.347).

Regier et al do not teach: 1) a combination of anti-CD52 antibody and interleukin-2 (IL-2) for treating CLL, 2) administration of CD52 antibody weekly or twice-weekly, and a total weekly dose of IL-2, 3) administration of anti-CD52 antibody and IL-2 by separate, sequential or simultaneous administration, or administration of a first dose of an IL-2 concurrent with or one week after a first dose of an anti-CD52 antibody and 4) initiation of one or more subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody at about 1 month to about 6 months following completion of a first cycle or completion of any subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody.

Kay et al teach using recombinant IL-2 for treating CLL because CLL is associated with deficiency in IL-2 (abstract, p.477, item under Discussion), and that IL-2 reduces growth of CLL (abstract).

Denis-Mize et al teach that a combination with IL-2 would improve the efficacy and durability of anti-cancer monoclonal antibody therapy (abstract, first two lines). Denis-Mize et al teach that interleukin-2 (Aldesleukin), which is used in phase I clinical trail of Non-Hodgkin's lymphoma, acts by increasing T cells and NK activity, such as NK-mediated antibody dependent cellular cytotoxicity (ADCC) and cytolytic killing, which is measured by standard 51Cr release assay (abstract).

Dmoszynska et al teach that administration of IL-2 in CLL induces a marked increase in T cell subsets and NK cells (abstract, p.337 and Tables II-III on p.337).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to combine anti-CD52 antibody taught by Regier et al with interleukin-2 taught by Kay et al for treating CLL, because: 1) CLL is associated with deficiency in the therapeutic IL-2 as taught by Kay et al, 2) A combination with IL-2 would improve the efficacy and durability of anti-cancer monoclonal antibody therapy, as suggested by Denis-Mize et al, because IL-2 acts by increasiing in the activity of T cells and NK activity, such as NK-mediated antibody dependent cellular cytotoxicity and cytolytic killing. Such increase in the activity of T cells and NK cells activity by IL-2 also occurs in CLL patients treated with IL-2, as taught by Dmoszynska et al, and 3) The two methods act by different ways and thus would complement each other, i.e, cancer cell killing via anti-CD52 antibody action versus increasing the immune response via increasing the activity of T cells and NK cells, which NK cells would mediate and thus enhancing the ADCC activity of the antibody used in the immunotherapy, in view of the teaching of Denis-Mize et al. One would have been motivated to do so to enhance the efficacy of CLL treatment.

Concerning the frequency and how anti–CD52 antibody and IL-2 are administered relative to each other, determination of optimum conditions is within the level of one of ordinary skill in the art. To determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

2. Claims 2-3, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Regier et al, Feb 2004, Leukemia & Lymphoma, 45(2): 345-349), in view of Kay et al, 1988, Nouv Rev Fr Hematol, 30: 475-478, IDS of 04/17/09, Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract only, and Dmoszynska et al, 1999, Leukemia & Lymphoma, 34(3-4): 335-340, IDS of 04/17/09, as applied to claims 1-2, 4-9, 11-13 above, and further in view of Mark et al (US 4,518,584, filed on 12/20/1983).

Claims 2-3, 9-10 are as follows:

2. (Original) The method of claim 1, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or a variant thereof having at least 70% sequence identity to the amino acid sequence for human IL-2.

3. (Original) The method of claim 2, wherein said variant thereof is des-alanyl-1, serine 125 human interleukin-2.

9. (Currently Amended) The method of claim 6, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or a variant thereof having at least 70% sequence identity to the amino acid sequence for human IL-2.

10. (Original) The method of claim 9, wherein said variant thereof is des-alanyl-I, serine 125 human interleukin-2.

The teaching of Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al has been set forth above.

Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al do not teach the use of anti-CD52 antibody with IL-2 variant or des-alanyl-1, serine 125 human interleukin-2 in treating CLL.

Mark et al teach making an IL-2 variant, des-alanyl-1, serine 125 human interleukin-2, where alanyl-1 is deleted and cysteine 125 is replaced with serine to eliminate intermolecular crosslinking or incorrect intramolecular disulfide bond formation (claim 4, and column 3, paragraph under "Modes for carrying out the invention""). Mark et al teach that des-alanyl-1, serine 125 human interleukin-2 (pLW46) has a higher IL-2 activity that of the native IL-2 control (column 18, Table II and paragraph under Table II).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to replace the native IL-2 in the combination of anti-CD52 antibody and IL-2 taught by Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al, with an IL-2 variant, des-alanyl-1, serine 125 human interleukin-2, taught by Mark et al, for enhancing the efficacy of treatment CLL, because des-alanyl-1, serine 125 human interleukin-2 is more advantageous than native IL-2, i.e., having higher IL-2 activity than native IL-2, in view of the teaching of Mark et al.

3. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Regier et al, Feb 2004, Leukemia & Lymphoma, 45(2): 345-349), in view of Kay et al, 1988, Nouv Rev Fr Hematol, 30: 475-478, IDS of 04/17/09, Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract only, as applied to claims 1-2, 4-9, 11-13 above, and Dmoszynska et al, 1999, Leukemia & Lymphoma, 34(3-4): 335-340, IDS of 04/17/09, and further in view of Ayanlar-Baturnan et al, 1986, Blood, 67(2): 279-284.

Claim 14. (Original) The method of claim 13, wherein T-cell counts are monitored in said subject to determine when each of said cycles is initiated, said cycles being initiated when T-cell

count is less than 80% of the T-cell count at the conclusion of any previous cycle of concurrent therapy with an IL-2 and an anti-CD52 antibody.

The teaching of Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al has been set forth above.

Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al do not teach monitoring T cell count to determine when each cycles of anti-CD52 antibody and IL-2 treatment is initiated, said cycles being initiated when T-cell count is less than 80% of the T-cell count at the conclusion of any previous cycle of concurrent therapy with an IL-2 and an anti-CD52 antibody.

Ayanlar-Baturnan et al teach that T lymphocytes of CLL patients are defective in IL-2 production (p.279, first column, third paragraph). Ayanlar-Baturnan et al teach that the response in CLL patients to IL-2 is measured by the increase in the T cell proliferation (abstract, first column).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to treat CLL, using the combination of anti-CD52 antibody and IL-2 taught by Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al, supra. It would have been obvious to monitor T cell count to determine when each cycles of anti-CD52 antibody and IL-2 treatment is initiated after the first cycle of treatment with anti-CD52 antibody and IL-2, because: 1) the response to IL-2 in CLL patients is measured by the increase in the T cell proliferation, as taught by Ayanlar-Baturnan et al, and 2) rIL-2 significantly increases the amount of T cells in treated CLL patients as taught by Dmoszynska et al.

Concerning initiation of anti-CD52 antibody and IL-2 treatment when T-cell count is less than 80% of the T-cell count at the conclusion of any previous cycle of concurrent therapy with

an IL-2 and an anti-CD52 antibody, determination of optimum conditions is within the level of one of ordinary skill in the art. To determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

4. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Regier et al, Feb 2004, Leukemia & Lymphoma, 45(2): 345-349), in view of Kay et al, 1988, Nouv Rev Fr Hematol, 30: 475-478, IDS of 04/17/09, Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract only, and Dmoszynska et al, 1999, Leukemia & Lymphoma, 34(3-4): 335-340, IDS of 04/17/09, as applied to claims 1-2, 4-9, 11-13 above, and further in view of Safar et al, 2000, Immunopharmacol, 49: 419-423.

Claim 15. (Original) The method of claim 6, wherein said total weekly dose of an IL-2 is in an amount that provides at least 50% of the NK stimulatory activity of a total weekly dose of Aldesleukin administered in a range of from about 1100 zig to about 1834 p. g.

The teaching of Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al has been set forth above.

Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al do not teach total weekly dose of an IL-2 is in an amount that provides at least 50% of the NK stimulatory activity of a

total weekly dose of Aldesleukin administered in a range of from about 1100 zig to about 1834 p. g.

Safar et al teach that Aldesleukin has been recommended by FDA for clinical treating cancer patients, such as metastatic renal and melanoma, and is also increasingly being widely used in innovative immunotherapic applications (abstract, p.419-420).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to treat CLL, using the combination of anti-CD52 antibody and IL-2 taught by Regier et al, Kay et al, Denis-Mize et al, and Dmoszynska et al, supra. It would have been obvious to use IL-2 in a concentration that stimulates NK activity, similar to that used for the mutant interleukin-2 Aldesleukin, such as in an amount that provides at least 50% of the NK stimulatory activity of a total weekly dose of Aldesleukin as a reference, because Aldesleukin has been recommended by FDA for clinical treating cancer patients, such as metastatic renal and melanoma, and is also increasingly being widely used in innovative immunotherapic applications, as taught by Safar et al, such as in Phase I clinical treatment of Non-Hodgkin's lymphoma, taught by Denis-Mize et al.

Moreover, determination of optimum conditions is within the level of one of ordinary skill in the art. To determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
March 20, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643

PTO/SB/21 (09-04)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

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Total Number of Pages in This Submission	
Attorney Docket Number	59516-313

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Deborah Hurst
Application No.	: 10/566,410
Filed	: January 30, 2006
For	: METHODS OF THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Docket No.	: 59516-313
Date	: April 16, 2007

Commissioner for Patents
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Respectfully submitted,
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Filing Date	January 30, 2006
First Named Inventor	Deborah Hurst
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U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,518,584	05-1985	Mark et al.	424/85.2
	B	US-			
	C	US-			
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	V	Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract
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minimal response (45% regression) has been observed in a patient with metastatic colorectal carcinoma, while 6 additional patients have had disease stabilization and have received 3 or more cycles of IL-12/pulse IL-2 (maximum 7 cycles and ongoing). Toxicities have been rapidly-reversible and non-dose-limiting through dose level 4. An episode of transient, but dose-limiting hypoxia was noted in a single patient treated on dose level 5, and enrollment for this dose level is ongoing. Notable toxicities have included constitutional symptoms such as fever, chills, and fatigue as well as hypotension, transaminitis and reversible leukopenia, neutropenia and lymphopenia among others. Evidence of potent immune activation is observed in treated patients including marked enhancement of circulating IFN-γ, IP-10 and IL-18 levels during the first week of therapy. Enhancement of ex vivo production of IP-10 by PBMC treated with PHA or IL-2 is noted in the majority of patients. **Conclusion:** This dose-intensive intravenous IL-12/pulse IL-2 regimen potently enhances immune activation in patients with advanced solid tumors, and has been well tolerated overall in patients treated to date.

Interleukin-2 (Proleukin®, Aldesleukin) Augmentation of NK-Mediated Antibody Dependent Cellular Cytotoxicity (ADCC) Is Associated with Durable Expansion of NK CD16$^+$CD56$^+$ Immune Effector Cells in Non-Hodgkin's Lymphoma Patients Receiving Rituximab

Kimberly Denis-Mize[1], Barbara Tong[1], William Larry Gluck[2], Alan R Yuen[3], Alexandra M Levine[4], Mark Dayton[5,6], Jon Paul Gockerman[7], Jennifer B Lucas[8], Sandra Milan[1], Deborah Hurst[1], *Susan E Wilson[1]*. [1]*Chiron Biopharmaceuticals, Chiron Corporation, Emeryville, CA;* [2]*Cancer Center of the Carolinas, Greenville, SC;* [3]*Stanford University Medical Center, Stanford, CA;* [4]*University of Southern California, Los Angeles, CA;* [5]*Louisiana State Medical Center, Shreveport, LA;* [6]*Parker Hughes Cancer Center, Roseville, CA;* [7]*Duke University Medical Center, Durham, NC;* [8]*California Cancer Care Department, Greenbrae, CA.*

New approaches are needed to improve the efficacy and durability of anti-cancer monoclonal antibody therapy. Accumulating data suggests that FcγR-mediated ADCC may be an important effector function associated with the efficacy of certain anti-cancer therapeutic antibodies. IL-2 induces the proliferation and survival of NK and T cells and facilitates the differentiation of effector functions including enhanced NK-mediated cytolytic killing (LAK) and augmentation of ADCC. Two Phase I clinical trials were conducted to assess the safety and tolerability of IL-2 administered subcutaneously, either daily or thrice weekly, in combination with rituximab for patients with Non-Hodgkin's Lymphoma. To further investigate the mechanism of IL-2 in these studies, secondary endpoint analysis included determination of lymphocyte subsets (CD3, CD4, CD8, CD16/CD56) and NK cell-mediated NK, LAK, and ADCC cytolytic function using a standard ^{51}Cr release assay with K562, Daudi or anti-CD20 coated Daudi cells as targets, respectively. Peripheral blood mononuclear cells were isolated from whole blood collected prior to rituximab treatment (Day 0), prior to IL-2 treatment (Day 8), during IL-2 administration on Days 15, 22, and 36, and five weeks after cessation of IL-2 treatment (Day 63). Although the majority of patients showed an increase in NK cell-mediated cytotoxic activity concomitant with IL-2 therapy, clinical responders exhibited a marked maintenance of both ADCC functional activity and increased NK cell number at Day 63, five weeks following the course of IL-2 immunotherapy. Normalization of NK cytolytic activity to NK cell number (CD3$^-$CD16/CD56$^+$) indicated that natural cytolytic and ADCC activities appear to be dependent on the total NK cell number as opposed to more potent cytolytic killing on a per NK cell basis. In contrast, LAK cytolytic function appeared to be independent of NK cell number. Collectively, these data suggest the combination of IL-2 and rituximab is a safe and tolerable approach to expand NK effector cells and augment ADCC.

Mechanisms of Escape

Role of Reactive Oxygen Species (ROS) on Death Receptors Signaling

Chulhee Choi[1,2], Eunjoo Jeong[1], Etty Benveniste[2]. [1]*Division of Molecular Life Sciences and Center for Cell Signaling Research, Ewha Womans University, Seoul, Republic of Korea;* [2]*Cell Biology, University of Alabama at Birmingham, Birmingham, AL.*

Tumor necrosis factors (TNF)-related apoptosis-inducing ligand (TRAIL), a member of the TNF/NGF family of cytokine, causes apoptosis via caspase activation in various cell types, especially transformed ones. We have previously shown that TRAIL induces caspase-dependent interleukin-8 (IL-8) expression as well as apoptosis in human glioma cells. Reactive oxygen species (ROS) have been regarded as secondary messengers in a variety of receptor-mediated signaling. We investigated whether ROS involves in TRAIL-induced signaling, apoptosis and IL-8 gene expression. In human astroglioma CRT-MG cells, we observed that 1) TRAIL increased intracellular level of ROS in a time- and dose-dependent manner; 2) pre-incubation with a non-specific caspase inhibitor, Z-VAD-fmk suppressed TRAIL-induced ROS generation, suggesting that generation of ROS is dependent on caspase activation; 3) pre-treatment with a ROS scarvenger NAC, or a flavoprotein inhibitor DPI suppressed intracellular levels of ROS generated by TRAIL ligation and augmented TRAIL-induced cell death; however 4) the same pre-treatment had no effect on TRAIL-mediated IL-8 mRNA expression. These results collectively suggest that TRAIL ligation increases levels of intracellular ROS, which can further inhibit caspase-dependent apoptosis but nor TRAIL-induced gene induction. Therefore, ROS can be regarded as a signal modulator in the Death Receptor-mediated signaling.

Expression of FC Gamma Receptor IIB by Melanoma Cells Modulates Tumor Growth and Therapeutic Effect of Monoclonal Antibodies

Joel FG Cohen-Solal, Lydie Cassard, Anshu Agarwal, Annie Galinha, Catherine Sautes-Fridman, Wolf Herman Fridman. *Laboratoire d Immunologie Cellulaire et Clinique, INSERM U255 UPMC-P6, Paris, France.*

We have shown that human malignant melanoma cells express the inhibitory low affinity Receptor for IgG's Fc, FcγRIIB1, in about 40% of tested metastases. Expression of human FcγRIIB1 (hFcγRIIB1) is associated with a profound inhibition of development of human melanoma tumors when grafted in the immunodeficient nude mice. This inhibition depends on anti-melanoma IgG3 antibodies and needs the intracytoplasmic tail of the receptor. Here, we have investigated the role of mouse FcγRIIB1 (mFcγRIIB1) expression on growth and uptake of B16F0 melanoma in immunocompetent mice. No significant effect of mFcγRIIB1expression was detected when tumor were grafted subcutaneously to C57Bl6 mice. However, mFcγRIIB1 expression in B16F0 profoundly inhibited the therapeutic effect of the anti-TRP1 MAb (TA99) on tumor growth.

Given that B16F0 melanoma is poorly immunogenic in syngeneic mice, tumor cells were grafted subcutaneously in allogeneic BALB/c mice to induce a strong immune response. Whereas B16F0 tumors were rejected by BALB/c mice, as well as B16F0 tumors expressing a mFcγRIIB1 mutated for the Tyr of the ITIM, the continuous growth of the mFcγRIIB1 expressing melanoma was observed in 50% of the mice. The existence of anti-tumor IgG was shown by the IgG dependent transfer of the protective effect of the serum of BALB/c mice bearing melanoma into SCID mice grafted by B16F0. In contrast to B16F0, the growth of B16F0 expressing the mFcγRIIB1 in SCID mice was insensitive to the protective effect of the serum.

Altogether this data reveal that mFcγRIIB1 oppose anti-tumor antibody based immunity or therapy and allow in vivo growth of murine melanoma cells. This

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Leukemia & Lymphoma, February 2004 Vol. 45 (2), pp. 345–349

Taylor & Francis healthsciences

Brief Report

Efficacy and Tolerability of Alemtuzumab (CAMPATH-1H) in the Salvage Treatment of B-Cell Chronic Lymphocytic Leukemia—Change of Regimen Needed?

K. RIEGER[a], U. VON GRÜNHAGEN[b], T. FIETZ[a], E. THIEL[a] and W. KNAUF[a,*]

[a]*Medizinische Klinik III, Universitätsklinikum Benjamin Franklin, Hindenburgdamm 30, 12200, Berlin, Germany;* [b]*Onkologische Schwerpunktpraxis Cottbus, Germany*

(Received 16 June 2003)

We report on the response rate and tolerability of Alemtuzumab (Campath-1H) in a series of heavily pretreated patients with B-CLL with a special focus on treatment-related problems. All patients tested positive for CD52 on B-lymphocytes before entering the trial. Thirteen patients with B-chronic lymphocytic leukemia (B-CLL), 1 prolymphocytic leukemia (PLL), 1 mantle cell lymphoma (MCL) and 1 leukemic immunocytoma (IC) transformed into a high-grade NHL were included. Median age was 62 years (range 40–73), and pretreatment consisted of median 3 prior regimens (range 1–11). All patients received 3, 10 and 30 mg of Campath-1H on sequential days, and then were subsequently scheduled for 30 mg 3 times weekly. Nine out of 16 patients responded. One patient attained complete remission (CR), 8 patients achieved partial remission (PR), while 4 patients had stable disease (SD). Three patients had progressive disease (PD). Beginning with initiation of treatment recurrent profound leukopenia became evident in 13 out of 16 patients leading to treatment discontinuation. Severe nonhematological toxicity (WHO grade IV bronchospasm) occurred in the first patient of this series, who initially had no concomitant steroids. Therefore, we developed a steroid co-medication regimen for the first 4 Campath-1H applications with quick tapering thereafter. Following this regimen, no infusion associated side effects WHO grade > II were observed. Infectious complications leading to treatment discontinuation consisted of pulmonary aspergillosis in one and bacterial pneumonia in another case. One patient with refractory B-CLL and *Pneumocystis carinii* pneumonia plus CMV reactivation died. In summary, Campath-1H appears to be effective against leukemic low-grade B-NHL, also in advanced stage. In our series, application 3 times weekly was not possible due to hematotoxicity. We recommend, therefore, flexible time intervals depending on the leukocyte counts. Whether a cumulative dosage according to 3 × 30 mg Campath-1H for 12 weeks is needed still remains to be clarified.

Keywords: Campath-1H; Alemtuzumab; Advanced leukemic B-NHL

INTRODUCTION

The humanized anti CD52 humanized monoclonal antibody Campath-1H is increasingly used as salvage regimen in the treatment of B-CLL and low-grade NHL. There are studies showing response rates to Campath-1H of 30–40% in extensively pretreated patients with B-CLL [1–4]. Many of those patients are reported as having received even more than 5 prior regimens, and therefore Campath-1H seems to be regarded as "the last therapeutical option". Patients with advanced stages of disease and with extensive prior treatment not only have a poor prognosis but also are known to be particularly vulnerable to infections and also to profound hematotoxicity probably because of a reduced bone marrow regenerating capacity.

The study presented here focusses on tolerability and efficacy of Campath-1H in a series of heavily pretreated patients with leukemic low-grade NHL and on the management of side-effects. Apart from the assessment of anti-lymphoma activity a major goal was to explore practicability and side effects of the intense treatment

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schedule of intravenous (i.v.) 3 × 30 mg Campath-1H weekly for 12 weeks recommended by others [1–4].

PATIENTS AND METHODS

Patient Characteristics

Thirteen patients with B-CLL (12 Binet stage C, 1 Binet stage B), 1 PLL, 1 MCL with extensive disease and 1 immunocytoma transformed into a high-grade NHL with a median age of 62 years (range 40–73) were analyzed. B symptoms were present in 10/16. A median of 3 prior regimens (range 1–11) have been applicated including fludarabine in 12 and anti-CD20 antibody Rituximab in 5 patients. Twelve patients suffered from thrombocytopenia, 8 of them had severe thrombocytopenia with platelet counts of less than 20/nl. Median leukocyte count was 44/nl (range 3.6–181). Twelve patients had splenomegaly (2 patients with B-CLL were splenectomized years ago), 11 patients suffered from enlarged lymph nodes, 4 with abdominal bulk. All patients were tested positive for the CD52-antigen on B-cells (median CD52 positive cells 81% (range 47–97) determined by flow-cytometry).

Treatment

Patients received 3, 10 and 30 mg of Campath-1H i.v. on sequential days and then were scheduled to receive 30 mg 3 times weekly for 12 weeks. Comedication consisted of paracetamol (1 g orally) and antihistamines (clemastin 2 mg i.v.), given 30 min before the infusions. The first patient who was treated without concomitant steroids experienced bronchospasm (WHO grade IV) shortly after the onset of the first Campath-1H application. Therefore, we developed a steroid co-medication regimen for the first 4 Campath-1H applications and quick tapering thereafter. The last 9 patients had prednisolone (2 mg/kg) during the Campath-1H escalation from 3 mg to 30 mg, followed by 1 mg/kg prednisolone for the fourth Campath-1H application. The fifth application was scheduled without prednisolone if there was no serious event before. Therapy was discontinued whenever hematotoxicity WHO grade III-IV occurred.

Prophylaxis against viral and bacterial infections consisted of aciclovir 4 × 400 mg p.o./day and cotrimoxazole (trimethoprim 160 mg, sulphamethoxazole 800 mg) twice daily 2 times each week over the period of therapy and the following 3 months. All patients were tested for pp65-antigen once weekly until the end of treatment, followed by routine monthly assessment for 3 months.

Response Evaluation

Response rates were evaluated according to 1996 NCI criteria [5]: CR is defined as freedom from clinical disease for at least 2 months with hemoglobin > 11 g/dl, neutrophiles $\geqslant 1.5 \times 10^9$/l, lymphocytes $\leqslant 4 \times 10^9$/l, and platelets $> 100 \times 10^9$ without transfusion, respectively. Additional CR criteria are: No constitutional symptoms present, no detectable lymphadenopathy, no hepatosplenomegaly as well as less than 30% small lymphocytes in the bone marrow without nodules. PR is defined by at least 50% reduction in the number of lymphocytes in the blood and at least 50% reduction in lymphadenopathy or hepatosplenomegaly or both. At least 1 of the following should be maintained for at least 2 months: hemoglobin > 11 g/dl or 50% improvement, platelets $> 100 \times 10^9$/l, neutrophils $> 1.5 \times 10^9$/l. PD is defined as lymphadenopathy, peripheral lymphocyte count, or hepatosplenomegaly increased by 50% or more or histology showing a more aggressive picture. Any response not falling into these categories is defined as SD.

RESULTS

Response

The median cumulative dose of Campath-1H was 343 mg (range 103–1,048), and was achieved after a median treatment-time of 10.5 weeks (range 1–18). In responders, a median of 433 mg Campath-1H (range 103–1,048) was given within a median of 10.5 weeks (range 3.5–18).

In our cohort of 16 patients, 1 patient with B-CLL (Binet B) who has had 2 prior chemotherapy regimens obtained CR, confirmed by bone marrow cytology plus flow-cytometry. Eight partial remissions were observed, while 4 patients had SD. One patient with PLL, 1 patient with B-CLL and 1 patient with IC had PD. (Patient characteristics and response rate are summarized in Table I).

Spleen size decreased in 8 out of 12 patients, lymph node size decreased $\geqslant$ 50% in 8 out of 10 patients. Abdominal bulk regressed by 20–50% in 4 out of 4 patients. Platelets increased in 4 out of 12 patients with pre-exisisting thrombocytopenia (3 of them with platelet counts < 20/nl) (Fig. 1). Median time to treatment failure was 20 weeks (range 20–45 weeks). Three patients with B-CLL stage Binet C were treated again with Campath-1H after a treatment-free period of median 17 weeks (range 15–19 weeks) due to disease progression. Two again achieved partial remission. The remainig patient, however, died with progressive disease after only 3 dosages of Campath-1H.

Three patients with chemotherapeutic refractory B-CLL Binet C achieved PR and could proceed to allogeneic transplantation. Time between conditioning with a toxicity-reduced regimen and last administered dose of Campath-1H was 7, 21 and 28 days, respectively. Two transplanted patients had very good PR and one achieved CR in the bone marrow 8 months after transplantation (Knauf, W. *et al.*, manuscript submitted).

TABLE I Patient characteristics and response rate

Patient number	Diagnosis[a]	Age [years]	Prior regimens [No.]	Cumulative dose [mg Campath-1H i.v.]	Response
1	B-CLL	61	11	733	PR
2	B-CLL	70	5	343	PR
3	B-CLL	63	3	253	PR
4	IC	67	3	133	PD
5	MCL	62	5	103	SD
6	PLL	68	1	133	PD
7	B-CLL	57	4	373	PR
8	B-CLL	54	6	433	PR
9	B-CLL	53	2	343	SD
10	B-CLL	60	3	193	PD
11	B-CLL	63	3	223	SD
12	B-CLL	67	2	1033	CR
13	B-CLL	66	4	343	PR
14	B-CLL	53	5	703	PR
15	B-CLL	73	2	233	SD
16	B-CLL	40	2	1048	PR

[a]B-CLL, B-chronic lymphocytic leukemia; PLL, prolymphocytic leukemia; IC, immunocytoma; MCL, mantle cell lymphoma.

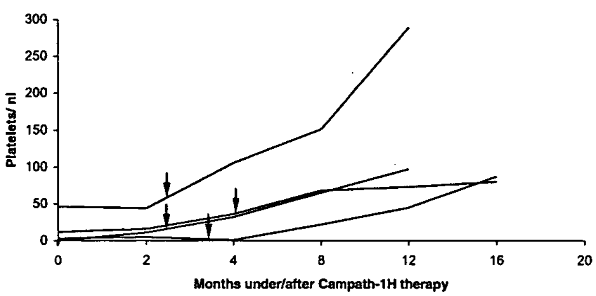

FIGURE 1 Increase of platelets in 4 (#1, 2, 14, 16) of 12 patients with pre-existing thrombocytopenia during and following Campath-1H therapy. Even after finishing Campath-1H treatment further increase of platelets could be seen. Arrows indicate last administered Campath-1H dose.

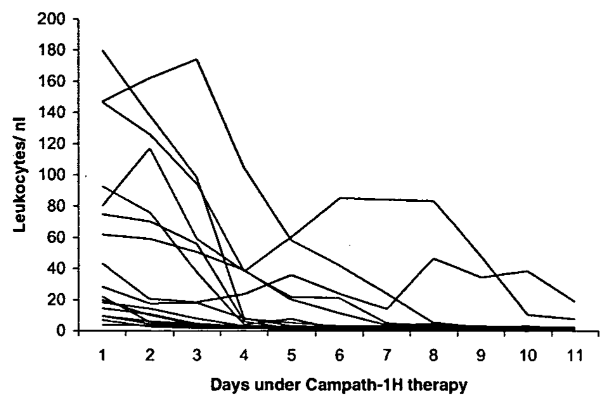

FIGURE 2 Leukocyte counts during the early phase of Campath-1H therapy in 16 patients. Leukocytes decreased from median 43.5/nl (range 3.6–181) to a median of 3.8/nl (range 1.7–104) within the first 4 days of Campath-1H therapy.

Hematotoxicity

Leukocytes showed a fast decrease under therapy independent of initial leukocyte counts, however, no tumor lysis syndrome was observed. Therapy had to be discontinued in 13 patients due to leukopenia WHO grade ⩾ III, with 9 patients experiencing leukopenia WHO grade IV within the first 2 weeks of treatment (Fig. 2).

While Campath-1H was stopped leukocytes increased to 1/nl within a median of 2 days (range 1–13) without G-CSF medication. Altogether, leukopenia led to treatment discontinuation for a median of 9 days (range 4–29). However, throughout the whole treatment period, recurrent leukopenia hampered a weekly application of 3 × 30 mg Campath-1H (Fig. 3). Only 2 patients completed the initially planned cumulative dose. One within the scheduled 12 weeks, whereas the other patient, reaching CR, had prolonged treatment of 18 weeks.

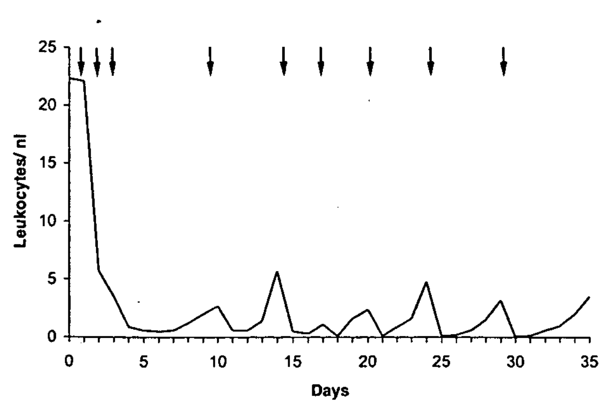

FIGURE 3 Leukocyte counts illustrating recurrent leukopenia of short duration, examplified in patient #10. Arrows indicate Campath-1H administrations.

Infusion-Related Toxicity

One severe bronchospasm (WHO grade IV) occurred in the first patient of this series who initially had no steroids as co-medication. The following patients were all treated with tapered doses of steroids. We developed a steroid de-escalation schedule that consisted of 2 mg/kg body weight prednisolone during the Campath-1H escalation from 3 mg to 30 mg, followed by 1 mg/kg body weight prednisolone for the fourth Campath-1H application. The fifth application was scheduled without prednisolone if there was no serious event before (Table II). Treating patient 8-16 according to this regimen, no severe infusion associated adverse events occurred. Three patients had an episode of rigor only during the first Campath-1H application (WHO grade II), while the following doses were well tolerated. One patient had rigor episodes (WHO grade II) despite steroid-comedication and was in need for additional pethidine.

Infectious Complications

Four patients had infectious complications leading to treatment discontinuation. We observed 1 pulmonary aspergillosis and 1 bacterial pneumonia. Death related to infections occurred in 2 patients with refractory disease: bacterial sepsis in 1 case and *Pneumocystis carinii* pneumonia (while prophylaxis was interrupted due to individual reasons) with concomitant CMV-reactivation in another case.

DISCUSSION

The anti CD52 monoclonal antibody Campath-1H is increasingly used in the treatment of NHL. There are numerous patients who had many chemotherapeutic regimens before Campath-1H became available. These patients often come to Campath-1H therapy when there is no more chemotherapeutical option.

TABLE II Schedule of steroid de-escalation during Campath-1H therapy

Day of i.v. Campath-1H application	Additional premedication with prednisolone [mg/kg body weight]	Campath-1H [mg]
day 1	2,0	3
day 2	2,0	10
day 3	2,0	30
day 5	1,0	30
day 7	–*	30
3 times weekly	–*	30

*Only if previous Campath-1H application showed no infusion-associated complications > WHO grade II.

Even though the scheduled cumulative dose of 1,033 mg Campath-1H was not reached in the majority of our patients due to hematotoxicity or infectious complications, overall response in these extensively pretreated patients was 9/16 (1 CR, 8 PR). Particularly, the response rate of lymph nodes was 80%. Regression of lymph nodes to Campath-1H therapy was previously described to be 30–36% in B-CLL [3,5] and only 5% in B-NHL [1]. We cannot exclude an additional effect of initial steroid co-medication to Campath-1H activity in our series. Interestingly, an overall response rate of 87% of peripheral lymph nodes has been described by Lundin *et al.* treating B-CLL patients with Campath-1H subcutaneously (s.c.) as first line therapy over a prolonged treatment period of 18 weeks [6]. Three patients in our series with chemotherapy-resistent disease (Binet stage C; 10, 12 and 15 years of disease) reached PR and underwent successful allogeneic stem cell transplantation thereafter. Enabling even heavily pretreated patients to be committed to allogeneic transplantation may be a particular option for Campath-1H that should be further assessed. Retreatment of 3 patients with B-CLL who initially reached PR led again to PR in 2 of them. This corresponds to a case report that described similar results [7].

Infusion related side effects consisted mostly of rigors. One severe bronchospasm (WHO grade IV) occurred in the first patient of this series who initially had no steroids as co-medication. It has been previously shown, that infusion-related toxicity occurs usually in the beginning of i.v. Campath-1H therapy and then decreases with time [2]. Therefore, we developed a steroid de-escalation regimen, which minimized the previously reported "first dose" reactions effectively. This concomitant premedication of prednisolone was limited to the dose escalation period of Campath-1H therapy and could reduce the risk of infusion associated events as well as steroid side effects. This short time steroid regimen may be also suitable for patients compromised by concomitant diseases like diabetes, osteoporosis and hypertension.

In the vast majority of our patients, the generally recommended application of 30 mg Campath-1H 3 times weekly as previously described [1–4] was not applicable throughout the whole treatment period due to hematotoxicity. Thirteen out of 16 patients had an episode of severe leukopenia (< 1/nl) and had recurrent leukopenias during therapy. We suggest that prolongation of therapy adapted to the leukocyte counts to a cumulative dose of about 1,033 mg could be a practicable guideline, although recovery of immune competence may be delayed accordingly. Nevertheless, in this series of patients an impressive remission rate was observed although the median administered cumulative dose was significantly lower than the doses reported by others [1–4]. The question arises, whether an individual response-adapted procedure could be an option.

Pharmacokinetic data derived from patients undergoing allogeneic bone marrow/stem cell transplantation

showed, that Campath-1H could be detected for 11–23 days after the administration of 50 mg split over 5 days or 100 mg split over 10 days, respectively [8]. Terminal half-life time was determined to be 15 and 21 days, respectively. This could explain our finding that even patients with repeated treatment discontinuation reached PR. Thieblemont *et al.* applied a maintenance therapy with monthly injections of Campath-1H in refractory B-CLL [9]. Despite longer treatment-free intervals, remissions were attained with less hematotoxicity. Moreover, in case of recurrent or prolonged leukopenia, a switch to s.c. application might be suitable. It has been described previously, that s.c. application of Campath-1H appears to be less hematotoxic [10]. An alternative approach to overcome episodes of leukopenia could also be G-CSF application.

In summary, we found Campath-1H effective in a series of heavily pretreated patients with leukemic low grade NHL. Surprisingly, remissions were reached with relatively low cumulative doses. Mode of application as well as treatment duration remain a matter of further investigation.

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Short communication

Interleukin 2 maintains biologic stability and sterility over prolonged time

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Abstract

The FDA approved interleukin 2 (IL2) for clinical use in 1992 in a high-dose bolus intravenous infusion schedule. IL2 administered by continuous low- and intermediate-dose infusion can result in a variety of immunologic effects including the expansion of the Natural Killer (NK) cell pool and immune reconstitution in immune-deficient hosts. These immune modifications are essential for augmentation of both currently available and evolving immunotherapies. The manufacturer's data indicate stability of the IL2 for a period of 6 days. This time frame is not practical for prolonged infusional schemes necessitating frequent changes of drug depots. We tested the biologic stability and sterility of the commercially available recombinant IL2 preparation (aldesleukin; Proleukin, Chiron) under clinical conditions for up to 30 days. Our results confirm that IL2 retains its biologic activity and sterility under these conditions for prolonged periods. This information will simplify IL2 outpatient regimens, allowing for convenient intervals for drug depot renewal, leading to improved patient compliance and conserved health care expenditures. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: IL2; Interleukins; Continuous infusion; Biologic stability

1. Introduction

The Food and Drug Administration approved interleukin 2 (IL2) for use in the United States for the treatment of patients with metastatic renal cell cancer and metastatic melanoma. Several schedules of IL2 administration have been explored in humans (Rosenberg, 1997). Most studies have used the bolus administration of IL2 at doses between 72 000 and 720 000 IU/kg per day (3–42 MIU/m^2 per day) intravenously every 8 h. IL2 has also been administered by continuous infusion at similar total daily doses. Prolonged continuous infusion allows a progressive increase in natural killer (NK) cells that is better than intermittent continuous infusions (e.g., every other week) or prolonged subcutaneous injections (Soiffer et al., 1992). NK cells have a central role in Antibody Dependent Cellular Cytotoxicity (ADCC). With the therapeutic availability of monoclonal antibodies, this role for IL2 is increasingly

Abbreviations: IU: international units; KIU: thousand international units; MIU: million international units

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being utilized for innovative immuno-therapeutic applications. Similarly, IL2 has been used for immune reconstitution in AIDS, with intermittent intravenous infusion for periods of up to 6–12 months (Kovacs et al., 1996). In patients with base-line CD4 counts above 200 cells per cubic millimeter, intermittent intravenous infusions of IL2 produced substantial and sustained increase in CD4 counts with no associated increase in plasma HIV RNA levels (Kovacs et al., 1996).

The registration trial and the manufacturer's (Chiron, Emeryville, CA) instructions included in the package insert calls for "administration of drug within 48 h of reconstitution". Internal documentation of the manufacturer confirms biostability of Proleukin for at least 6 days under clinical conditions (data on file with FDA). The 6-day stability standard is not problematic in the high-dose and intermittent regimens, but it creates substantial logistical obstacles to patients and nursing staff involved in the outpatient continuous intravenous infusion schedules, that necessitate drug changes on a basis of shorter than a 1-week interval. Additionally, increased costs result from more frequent utilization of pharmacy and clinic facilities on such 6-day or shorter renewal interval regimens.

In the present study, we examined the stability of the biologic activity of IL2 (Proleukin, Chiron) and its sterility over extended time periods. This study proves adequate biologic stability and sterility for an interval of at least 30 days, thereby enabling more prolonged infusion periods without interruptions, and simplifying outpatient delivery of the drug.

2. Materials and methods

2.1. IL2 preparation

IL2 sample was reconstituted in 5% Dextrose (D5W, USP) according to the manufacturer's instruction to create a final concentration of 200 KIU/ml, and stored in a standard infusion plastic bag [Viaflex, Baxter, Deerfield, IL]. The sample was maintained at 31°C (88°F) to exceed the mean temperature of an externally carried pump reservoir. Aliquots on days 1, 8, 15, 21, and 30 were obtained under aseptic conditions and immediately stored at −80°C. These aliquots of IL2 were then evaluated for bioactivity using the standard IL2 bioassay.

2.2. IL2 bio-assay

The assay has been described in detail elsewhere (Gillis et al., 1978). The standardized IL2 dependent murine T-lymphocyte cell line CTLL-2-(American Type Culture Collection, Rockville, MD) was routinely used for this cytokine assay. It has been shown that with increasing IL2 in the medium, increasing proliferation of these cells ensues, as evidenced by the increasing incorporation of tritiated thymidine into cellular DNA. To begin, assay cells were washed free of growth medium and resuspended in RPMI 1640 (Cellgro), supplemented with 10% fetal calf serum. For the standard curve, serial dilutions of IL2 in four replicas were made in a 96-well plate (Costar-Corning, NY), and CTLL-2 cells then added and incubated at 37°C in a humidified atmosphere of 5% CO_2 in air. After 24 h, ^{3}H-thymidine was added (1 μCi per well) and cells were allowed to proliferate for an additional 6 h. Cells were then harvested onto a fiberglass filter strip (PHD Harvester, Brandel, Gaithersburg, MD) and ^{3}H-thymidine incorporation was determined as previously described (Oppenheim, 1976). The incorporation (CPM) was plotted against the corresponding IL2 concentration to generate a standard curve. Filter counts in the absence of IL2 added to medium were subtracted as background.

IL2 to be tested in this experiment from all aliquots drawn at different time points was diluted in RPMI 1640 medium to approximate a final concentration of 4 IU/ml corresponding to the linear portion of the assay standard curve. Each sample aliquot was tested in three replicas.

2.3. Sterility testing

After day 30, samples from two separately prepared bags were obtained under aseptic condition and submitted to the Microbiology Department in air-evacuated sterile containers (Vacutainer, Becton Dickinson, Franklin Lakes, NJ). Cultures were requested for aerobic, anaerobic and fungal organisms.

Results were reported after 14-day incubation for the bacterial cultures and 30-day for the fungal cultures.

3. Results

IL2 was maintained in a controlled temperature environment of 31°C to exceed typical conditions of external infusion pumps. Aliquots of this sample were obtained on days 1, 8, 15, 21, and 30, and immediately stored at $-80°C$ for subsequent testing.

3.1. IL2 bioactivity

IL2 bioactivity is tested in this experiment by measuring the thymidine incorporation in a well-defined standard murine T-lymphocyte cell line, CTLL-2. This cell line reproducibly proliferates in the presence of IL2 in a dose-dependent fashion, with increasing incorporation of ^{3}H-thymidine. When incorporation is plotted against the different IL2 concentrations, a standard curve is generated. This assay was used to compare the bioactivity of standard IL2 (day 1) to that of IL2 obtained after an incubation period at 31°C (days 8, 15, 21, and 30). The mean scintillation counts observed from these different IL2 samples after dilution are depicted in Fig. 1. All samples were within the linear range of the standard curve (not shown). These results reveal that samples drawn on days later than day 1 yield similar incorporations, confirming the biostability of IL2 over the entire time period tested. Similarly, full dilution curves were prepared from day 1 IL2 and day 30 IL2 and showed no significant difference in activity over the dilution range (Fig. 2). Our results indicate that the bioactivity of the IL2 (aldesleukin; Proleukin, Chiron) as prepared here remains stable for at least 30 days.

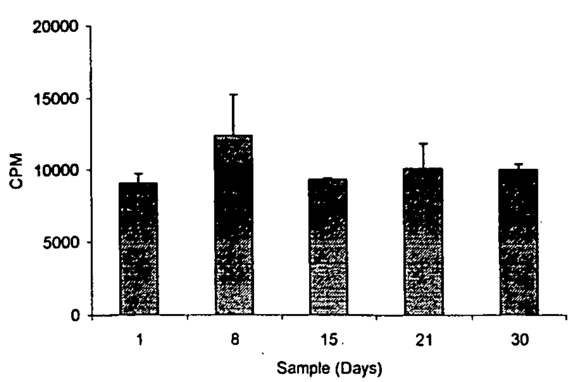

Fig. 1. Stability of IL2 bioactivity. Thymidine (^{3}H-thymidine) incorporation [CPM] in samples prepared at different time points. Note that no sample has shown "less" incorporation when compared to the standard sample from day 1.

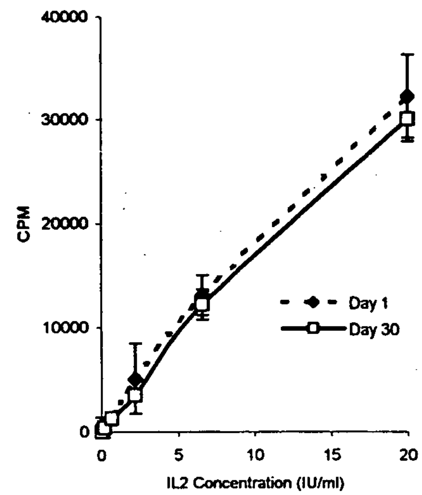

Fig. 2. Lymphokine bioassay comparing bioactivity of IL2 at day 30 incubation with the standard day 1 IL2 (mean ± SD).

3.2. Sterility

Sterility testing was achieved by submitting samples to the institution's microbiology laboratory after day 30. Duplicate samples were withdrawn from each of the two separately prepared bags with IL2. No colonies were identified, and all cultures (aerobic, anaerobic and fungal) were reported as "sterile". Our results indicate that IL2 (Proleukin–Chiron) as prepared here remains sterile when incubated at 31°C for at least 30 days.

4. Discussion

IL2, a lymphokine produced by activated T cells, has a wide variety of actions and plays a central role in immune regulation (Smith, 1988). The primary action of IL2 is its ability to stimulate the growth of activated T cells and natural killer cells that bear IL2

receptors, although IL2 has a variety of other actions on T cells, B cells, macrophages, epidermal Langerhans cells, and oligodendroglia (Rosenberg, 1997). The mature protein consists of 133 amino acids and has a predicted molecular weight of 15 420 Da.

Many of the actions of IL2 suggested that this molecule might be of value in cancer therapy. Adoptive immunotherapy — the transfer of cells with antitumor activity to the tumor-bearing host — has substantial therapeutic attractiveness as an approach to treating human cancer, and is improved in antitumor efficacy by the co-administration of the IL2 (Rosenberg, 1997). Similarly, with the advent of monoclonal antibodies in the treatment of cancer, augmentation of the effects of these approaches is becoming increasingly relevant.

IL2 can be administered in the outpatient setting by a variety of methods. These include different schedules of continuous i.v. infusion, interrupted i.v. infusion, or subcutaneous daily injections (Meropol et al., 1996; Soiffer et al., 1992; Sosman et al., 1991). Prolonged continuous infusion, via portable pump and indwelling venous access, allows a progressive increase in NK cells that is better than intermittent continuous infusions (e.g., every other week) with higher doses (Kohler et al., 1989; Caligiuri et al., 1993). Furthermore, in vitro data suggests that maximal stimulation of peripheral blood lymphocytes by IL2 requires — in addition to the presence of the IL2 receptor on the cell surface — prolonged exposure of these cells to IL2 (Kohler et al., 1989; Soiffer et al., 1994). Accordingly, prolonged infusion regimens may be the optimal schedule for IL2 as immune adjunct. Outpatient dosing is feasible, and doses up to 72 000 KIU/kg per day (3 MIU/m^2 per day) for 4 days by continuous infusions was tolerated with no toxicity greater than grade II (Sosman et al., 1995). Long term (3 months) outpatient continuous infusions were tolerated at 43 000 KIU/kg per day (1.8 MIU/m^2 per day) (Caligiuri et al., 1991), and regimens of 145 000 KIU/kg per day [6 MIU/m^2 per day] for up to 2 months (H. Koon, A.M. Safar, P. Severy, R.P. Junghans, unpublished data).

Our goal in this study was to test the biologic stability and sterility of the commercially available IL2 (aldesleukin; Proleukin, Chiron) when prepared according to manufacturer's guidelines. Biostability was shown using a conventional cytokine bioassay, as described in Materials and methods. In this type of evaluation, it is essential to apply a bioassay instead of an ELISA-type assay which could detect protein that might have lost its biologic activity.

Our study shows that IL2 remains stable and sterile in conditions appropriate to outpatient continuous intravenous infusion for prolonged periods of time (up to 30 days). This will simplify IL2 clinical use as an immune adjunct by allowing convenient drug depot renewal intervals of as long as 1 month. Continuous infusions of IL2 may be applied in cancer to enhance T-cell and NK therapies. Similarly, in immunodeficient states such as AIDS, chronic, prolonged administration of IL2 is being tested, and will be greatly facilitated by extending renewal intervals up to one month for such infusions. This is an important result that will enable administration of this cytokine by intravenous infusion for prolonged periods which should result in decreasing need for changes in "drug depot" and outpatient utilization. This will undoubtedly improve patient compliance, and conserve health-care dollars.

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Interleukin-2

A Review of its Pharmacological Properties and Therapeutic Use in Patients with Cancer

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Summary

Synopsis

Recombinant interleukin-2 (IL-2) products (e.g. aldesleukin, teceleukin) are nonglycosylated, modified forms of the endogenous compound. IL-2 acts as a pleiotropic mediator within the immune system, having a variety of effects via specific cell surface receptors. The interaction of IL-2 with the IL-2 receptor induces proliferation and differentiation of a number of T lymphocyte subsets, and stimulates a cytokine cascade that includes various interleukins, interferons and tumour necrosis factors. Antitumour effects of IL-2 appear to be mediated by its effects on natural killer, lymphokine-activated killer (LAK) and other cytotoxic cells. In vivo *and* in vitro *effects of IL-2 seem to be dependent to a large extent on the environment; many studies have reported conflicting results, perhaps due to diverse populations of effector cells, the availability of other cytokines that have synergistic or inhibitory influences, and the dosage regimens used. The recombinant products appear to be biologically indistinguishable from native IL-2* in vitro *and* in vivo*; the former induce minor antibody formation but this does not appear to alter functional properties.*

In patients with metastatic renal cell carcinoma, IL-2 therapy achieves average objective response rates of 20% (range 0 to 40%), with a complete response rate of about 5% (range 0 to 19%). Response duration varies considerably but can be durable (lasting for >12 months), with some patients remaining in complete response for >60 months. It is unclear at present whether higher dosage regimens improve clinical response, or whether combination therapy with other agents and/or adoptive therapy is beneficial. Survival duration may depend on the risk factors present, with poorer performance status and more than one site of metastases associated with shorter survival times. Patients with metastatic malignant melanoma receiving IL-2 as monotherapy show an average objective response rate of 13% (range 3 to 24%); however, objective response rate averages 30% (range 4 to 59%) when IL-2 is used in combination with other agents. Overall median survival appears to be about 10 months. Preliminary data indicate that IL-2 produces a lower response rate in patients with refractory colorectal carcinoma, ovarian cancer, bladder cancer, acute myeloid leukaemia or non-Hodgkin's lymphoma. Adverse effects accompanying high dose, intravenous IL-2 therapy can be severe, with cardiovascular, pulmonary, haematological, hepatic, neurological, endocrine, renal and/or dermatological complications frequently requiring doses to be withheld. Typically, these effects resolve rapidly with cessation of IL-2 therapy, and may be reduced considerably with regional or subcutaneous administration.

In conclusion, IL-2 offers hope to some patients with renal cell carcinoma, malignant melanoma and other neoplastic disease, but appropriate patient selection and optimum dosage regimens

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are at present unresolved. Establishment of reliable predictors of clinical response, and optimum dosage schedules and methods of administration should enable a better assessment of the place of IL-2 in the treatment of these patients.

Pharmacological Properties

Interleukin-2 (IL-2) is an autocrine and paracrine biological response modifier, and recombinant IL-2 products (e.g. aldesleukin, teceleukin) appear to have essentially identical action to the endogenous molecule within the body. IL-2 promotes B and T cell proliferation and differentiation, and initiates a cytokine cascade that has both inhibitory and synergistic effects on IL-2 activity. Most effects are mediated via the IL-2 receptor, which is expressed in increased amounts on activated T cells. The *in vitro* antitumour effects of IL-2 are thought to occur via increased proliferation of natural killer, lymphokine-activated killer (LAK), and other cytotoxic cell populations. IL-2 has been co-administered with a number of other cytokines; however the results so far are inconclusive, and in many instances, conflict with the *in vivo* data.

In patients, the most common pharmacological effects of IL-2 therapy appear to be eosinophilia, acute lymphopenia followed by rebound lymphocytosis, and induction of LAK and natural killer cell activity. Increases in the levels of other cytokines have been reported, e.g. interleukins-3, -4, -5, -6 and -8, tumour necrosis factors-α and -β and interferon-γ, although other investigators dispute these findings, perhaps due to differing dosage schedules and sampling times. Changes in immune responses have been noted, but antibodies formed to recombinant products did not appear to interfere with biological activity. Other effects include alterations in plasma hormone levels (e.g. increase in atrial natriuretic factor and adrenocorticotropic hormone levels, decrease in melatonin levels) and other serum components (e.g. decrease in cholesterol, factor XII and prekallikrein levels, increase in biopterin levels).

The formulation of IL-2 may affect its pharmacokinetic properties; however, most non-glycosylated recombinant products appear to have similar pharmacokinetic profiles. Clearance occurs predominantly via the kidney, and appears to be biphasic.

Therapeutic Use

Approximately 20% of patients with metastatic renal cell carcinoma, and 13% of patients with malignant melanoma achieve objective responses with IL-2 monotherapy. Approximately 5% of patients with renal cell carcinoma achieve complete response (complete disappearance of all measurable disease), which is durable in many instances, persisting for >12 months, and in some patients for >60 months. Overall median survival approximates 10 months; however, it appears that survival may be correlated with the performance status of the patient, the duration from diagnosis to trial entry, and the number of metastatic sites.

Complete response rates in patients with malignant melanoma receiving IL-2 monotherapy are low (approximately 2.5%) but show a similar durability to those seen in patients with renal cell carcinoma. Adoptive immunotherapy, with autologous LAK cells or tumour-infiltrating lymphocytes (TIL) that have been activated *ex vivo* and then reinfused during IL-2 therapy, does not appear to improve the clinical response. Combination therapy of IL-2 with conventional chemotherapeutic agents or with interferon-α (IFN-α) does not appear to improve response in patients with renal cell carcinoma, but combination chemotherapy and immunotherapy with IL-2 and >1 agent appears to be advantageous in patients with malignant melanoma. Objective response rates average 36% (range 4 to 59%), with complete response rates of approximately 7%.

Patients with colorectal cancer are likely to respond to IL-2 therapy combined with chemotherapy with objective response rates of about 10%. The therapeutic value of IL-2 therapy in patients with bladder or ovarian cancer, non-Hodgkin's lymphoma or acute myeloid leukaemia remains to be established. At present, there is little conclusive evidence to support an optimum dosage regimen or method of administration.

Although much research has attempted to detect reliable markers of clinical response, results of studies are conflicting. Levels of circulating IL-2 are unlikely to be associated with clinical response. The presence of raised levels of C-reactive protein and interleukin-6 (IL-6) have been associated with a poorer prognosis. It is thought that patients' human leucocyte antigen (HLA)

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haplotype and lymphocyte subset population sizes may have a role in determining response, but further work is required to clarify this issue.

Tolerability

Adverse effects associated with IL-2 may be severe and affect most organ systems, but tend to be rapidly reversible with cessation of therapy. Toxicity appears to be dose-dependent, and can be reduced considerably with local or subcutaneous administration. A major concern, particularly with high-dose intravenous regimens, is capillary leak syndrome. This manifests with hypotension requiring vasopressor support in 70% of patients, weight gain that is often >10% of bodyweight, acute renal failure, pulmonary congestion and dyspnoea, and is reminiscent of early septic shock. Other complications include neurological abnormalities and psychiatric disorders, myocardial toxicity, hepatic and thyroid dysfunction, coagulation disorders and haematological complications, and dermatological effects. Patients receiving systemic IL-2 have an increased risk of infection, and sepsis was a major cause of death before the routine use of prophylactic antibiotics was implemented. Mortality has been 1 to 6% in reported trials; however, it is hoped that guidelines for patient selection will considerably improve tolerability in future trials.

Dosage and Administration

Many different dosage schedules and methods of administration have been used with IL-2 therapy. In the US in patients with renal cell carcinoma, 6×10^5 IU/kg given intravenously as a 15-minute bolus every 8 hours for up to a total of 14 doses is recommended, followed by a further cycle after a variable interval. The recommended rest period is 9 days, but intervals of 3 days to several weeks have been used in clinical trials. Doses are usually withheld rather than reduced when toxicity is evident. In Europe the approved dosage regimen is continuous infusion of 18×10^6 IU/m^2/day for two 4.5- to 5-day cycles, with a rest period of about 6 to 8 days.

Subcutaneous and regional administration methods have been used in patients, but recommendations for dosage and scheduling have not been made. In combination therapy the dosages of IL-2 are often reduced. Although intensive monitoring is often required with bolus dosage regimens, IL-2 has been administered subcutaneously in an outpatient setting.

This review evaluates the place of interleukin-2 (IL-2) in the treatment of metastatic renal cell carcinoma and malignant melanoma, and considers preliminary studies in the treatment of colorectal, ovarian and bladder cancers, non-Hodgkin's lymphoma and acute myeloid leukaemia. Due to the extensive number of studies performed with IL-2, this review has been necessarily limited to monotherapy and combination therapies currently or previously used in clinical trials in patients with these primary diagnoses. Aldesleukin, teceleukin and other types of interleukin-2 have also been used in patients with a variety of other disorders (see table I) which are beyond the scope of this review. Similarly, the activity of IL-2 in animal models has been extensively reviewed elsewhere (Albertini et al. 1992; Kintzel & Calis 1991; Winkelhake & Gauny 1990), and as this review is focused on the clinical use of IL-2, animal studies are briefly mentioned only where data in humans are lacking.

IL-2 products in current use are mainly recombinant human interleukin-2, produced using a cloned modified gene in bacteria, usually an *Escherichia coli* strain. Several varieties of recombinant IL-2 have been produced, with different substitutions at the N-terminal and/or at amino acid 125, and with diverse formulations (table II). In many reports the product under investigation is not specified. Furthermore, despite the lack of studies comparing the different products, it is assumed that they have similar pharmacological activity and tolerability profiles. An exception to this is polyethylene glycol-modified interleukin-2 (PEG-IL-2), which, in the limited studies reported so far, appears to have a reduced immunogenicity and altered pharmacokinetic properties (Katre 1990). In this review

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Table I. Alternative indications for interleukin-2 therapy. A list of representative clinical studies and the predominant diagnoses of evaluable patients[a]

Indication	Reference
Atopic dermatitis	Hseih et al. (1991)
Bone marrow transplantation	Blaise et al. (1991); Bosly et al. (1992); Higuchi et al. (1989); Négrier et al. (1991a); Soiffer et al. (1992)
Breast cancer	Dalgleish et al. (1990); Israel et al. (1989); Spicer et al. (1992)
Epstein-Barr virus infection	Komiyama et al. (1989)
Gastric cancer	Ubhi et al. (1992)
Hepatitis B infection	Yamaguchi et al. (1988) Zeniya et al. (1991)
HIV infection	Flad et al. (1986); Gramatzki et al. (1986); Klimas (1992); Krigel et al. (1989); McElrath et al. (1990); Schwartz et al. (1991); Wood et al. (1993)[b]
Insulin-dependent diabetes mellitus	Carnazzo et al. (1989)
Lepromatous leprosy	Converse et al. (1990); Kaplan et al. (1991)
Liver cancer	Chien et al. (1991); Ito et al. (1989); Onishi et al. (1989); Yamamoto et al. (1993)
Lung cancer	Clamon et al. (1993); Jansen et al. (1992); Lissoni et al. (1992e); Yang et al. (1991); Yasumoto & Ogura (1991)
Malignant glioma	Merchant et al. (1988); Merchant et al. (1992); Yoshida et al. (1990)
Neuroblastoma	Favrot et al. (1989)
Perioperative immunotherapy for cancer	Nichols et al. (1992)
Squamous cell carcinoma of the head and neck	Gore et al. (1992); Mattijssen et al. (1991); Schantz et al. (1991); Squadrelli-Saraceno et al. (1990)

a Studies that included a heterogeneous patient population (with a variety of different diagnoses) have been omitted.
b Patients received polyethylene glycol-modified interleukin-2 (PEG-IL-2).

the term 'interleukin-2' (IL-2) will be used where the product in question is not clearly defined as PEG-IL-2.

Biological activity of IL-2 *in vitro* is indistinguishable from that of the endogenous compound, and clinical pharmacodynamics are similar (Pawelec et al. 1991); although some *in vivo* differences in antibody formation have been noted (Schwuléra et al. 1992). IL-2 is phosphorylated by protein kinase C *in vitro* without affecting the biological activity. The physiological role of this phosphorylation remains unclear (Kung et al. 1989), although tyrosine kinases are implicated in the signal transduction induced by IL-2 (Minami et al. 1992; Smith 1993).

1. Pharmacological Properties and Role in the Immune System

Interleukins are so named because they are a molecular means of communication between leucocytes. IL-2, previously known as 'T cell growth factor', is a 15kD glycoprotein produced by T helper cells following activation by interleukin-1 (from macrophages) and an antigen. It has autocrine and paracrine activity, stimulating T helper, cytotoxic and suppressor cell activity, as well as B cells, natural killer cells and cytotoxic macrophages. IL-2 induces a cytokine cascade, with increased production of tumour necrosis factors (TNF), interferons (IFN) and interleukins (IL) *in vitro* and *in vivo*. Thus, IL-2 is a pleiotropic mediator, exerting multiple effects via specific receptors expressed on a wide variety of cells (fig. 1).

1.1 Mechanism of Action – the IL-2 Receptor

T cells become activated in the presence of IL-1 or IL-6, following recognition of antigen presented by major histocompatibility complex (MHC) molecules [or the equivalent leucocyte antigens in humans (HLA)] on the surface of antigen-presenting cells (usually macrophages). Activated T cells

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produce IL-2, and simultaneously express the high-affinity IL-2 receptor. Cells that are capable of producing IL-2 when stimulated have membrane-associated IL-2 epitopes on the cell surface, which are not present when the cell is actively secreting IL-2 (Kaplan et al. 1988).

The IL-2 receptor is composed of at least 3 protein chains: a low-affinity receptor 55kD protein (p55, or α-chain), and an intermediate-affinity receptor composed of 75kD (p75, or β-chain) and 64kD (p64, or γ-chain) proteins. The low- and intermediate-affinity receptors combine to form a high-affinity receptor (fig. 2). Other cytoplasmic proteins are also thought to be implicated in high-affinity receptor formation and subsequent signal transduction (reviewed in Minami et al. 1992; Smith 1993; Taniguchi & Minami 1993). IL-2 binding to high-affinity receptors on activated T cells is necessary for the induction of proliferation of these cells, and IL-2 binds to 2 distinct sites on the p55 and p75 chains (Debatin et al. 1989). Cells expressing the p55 chain on their cell surfaces are referred to as Tac+, and 'anti-Tac' monoclonal antibodies block the interaction between IL-2 and its receptor (Oh-Ishi et al. 1989). Anti-Tac inhibited the generation of T suppressor cells in response to IL-2, in both antigen-specific and antigen-nonspecific systems *in vitro* (Oh-Ishi et al. 1989). However, some actions of IL-2 may not be mediated by high-affinity receptors, as anti-Tac did not inhibit IL-2-induced activation of large resting granular lymphocytes into effective natural killer

Table II. Comparison of interleukin-2 products[a]

Name of compound (manufacturer)	Production	Component alterations	IU	Cetus units	Nutley units	BRMP units	Formulation
Aldesleukin (Cetus)	*Escherichia coli*	125 Serine, no amino-terminal alanine, no glycosyl units	6[b]	1[b]	2[b]	2	1.1 mg/ml (18 × 10^6 IU) in 50mg mannitol, 0.18mg SDS, sodium phosphate buffer. Lyophylised powder, reconstituted in sterile water. Specific activity 18 × 10^6 IU/mg protein
Teceleukin or r met IL2 (Hoffman La-Roche)	*Escherichia coli*	Methionine added at amino-terminal, no glycosyl units	3[c]		1	1	1 MU + 0.25% human serum albumin. Lyophilised powder, reconstituted in isotonic saline. Specific activity 12-15 x 10^6 BRMP Units/mg protein
Bioleukin (Glaxo)		125 Alanine, amino-terminal methionine	2?				Specific activity 10-17 x 10^6 IU/mg protein

a Other products under development include glycosylated interleukin-2 from cultured human monocytes, polyethylene glycol-modified interleukin-2, and other recombinant non-glycosylated agents with alterations at amino acid 125 and/or the amino terminal. However, full details of activity and formulation are unobtainable at present. To date, only aldesleukin is commercially available.

b Data obtained from Richards and Lotze (1992). Literature sources of unit information are occasionally conflicting, possibly due to modification of the lymphocyte bioassays used to determine activity.

c Literature sources differ considerably e.g. Vlasveld et al. (1992), Roper et al. (1992). These unit conversion factors have therefore been based on the comparative clinical efficacy with aldesleukin (personal communication, Dr Lauper, Cetus Corporation).

Abbreviations: BRMP = biological response modifier protein; IU = international units (as determined by a lymphocyte proliferation assay); MU = million Nutley units; SDS = sodium dodecyl sulphate.

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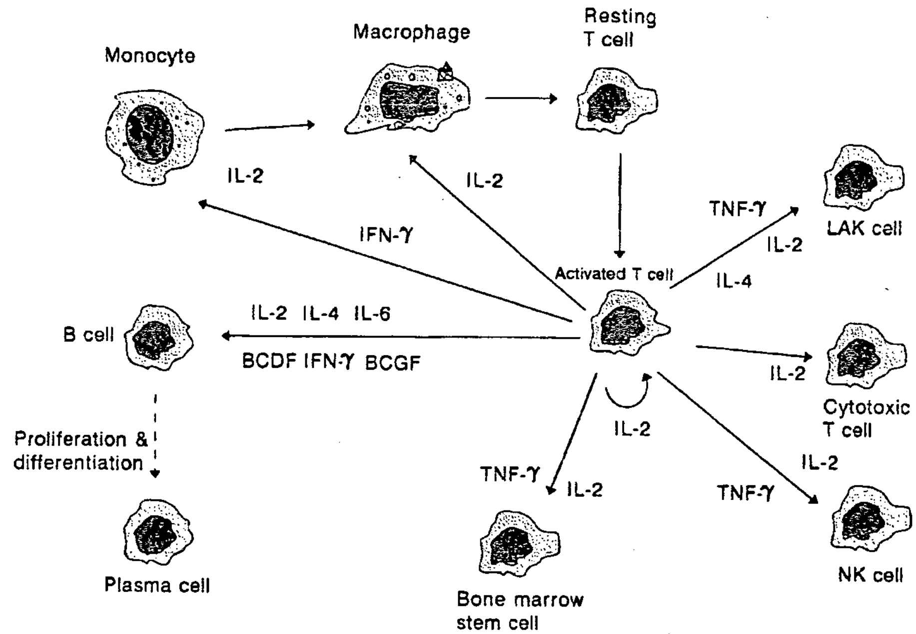

Fig. 1. Role of interleukin-2 (IL-2) within the immune system. The figure indicates probable interactions and outcomes of IL-2 therapy. *Abbreviations:* BCDF = B cell differentiating factor; BCGF = B cell growth factor; IFN = interferon; IL = interleukin; LAK = lymphokine-activated killer; NK = natural killer; TNF = tumour necrosis factor.

cells (Oh-Ishi et al. 1989). It has been suggested that the presence of the p75 chain on these cells may be sufficient to cause natural killer cell proliferation when relatively high concentrations of IL-2 are present (Minami et al. 1992). IL-2 receptors have not been found on cells that are not activated by IL-2 (Nakanishi et al. 1989), but resting T cells, natural killer cells and large granular lymphocytes express the p75 chain. Although IL-2 first associates with the p55 chain, the internalisation of IL-2 and the signal inducing cellular proliferation are correlated with IL-2 binding to the p75 chain (Robb & Greene 1987; Wang & Smith 1987). The induction of p55 chain and p75 chain proteins appears to be regulated by different cytokines, with IFN-γ inducing p55 chains at the transcriptional level, and IL-2 inducing p75 chains at the post-transcriptional level in human monocytes (Espinoza-Delgado et al. 1992). Interestingly, soluble low-affinity IL-2 receptors have been detected in the circulation of both animals and humans undergoing IL-2 therapy (Barton et al. 1993; Lim et al. 1991d; List et al. 1992; Spiers et al. 1993). The likelihood that this mechanism causes immunosuppression is debatable, although it may also be linked in some way to antitumour response (see section 1.3.4).

1.2 *In Vitro* Effects

1.2.1 Cell Proliferation and Differentiation

Interaction of IL-2 with the IL-2 receptor induces T cell proliferation and differentiation. High affinity IL-2 receptors are coupled to tyrosine kinase activity in T cells *in vitro* (Augustine et al. 1990), and IL-2-dependent kinase activation correlates with G_1 to S-phase transition in the T cell cycle (Morice et al. 1993). In addition, cyclic AMP, phospholipase D and the formation of phosphatidic acid have a role in the signal transduction by

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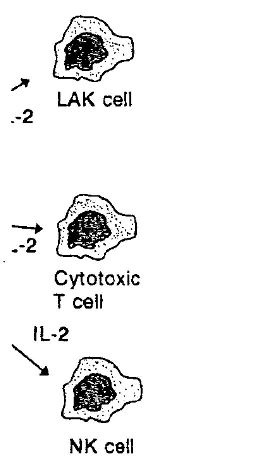

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IL-2 (Cano et al. 1992; Wickremasinghe et al. 1987), and the mitogenic effect of IL-2 on T cells may depend on the presence of monocytes (Mookerjee & Pauly 1989). IL-2 does not act via GTP-binding protein, despite increased cyclic AMP levels (Moscovitch-Lopatin et al. 1991). *In vitro* studies suggest that IL-2 increases the activity of the Na^+/K^+-ATPase pump of cytotoxic lymphocytes, and that this activation is related to subsequent cell growth (Redondo et al. 1986). T cells activated *in vitro* or *in vivo* with IL-2 bind complement, a reaction amplified by IL-2-induced C-reactive protein (Vachino et al. 1991). Marked complement activation has been noted during and after IL-2 therapy, without the usual accompanying neutrophil activation (Moore et al. 1991). Changes in glutathione concentration may modify the activity of IL-2, as increased levels of glutathione *in vitro* accelerated the internalisation of IL-2 and enhanced the proliferation of cytotoxic T cells (Liang et al. 1989).

A proliferative response to IL-2 has also been observed with activated B cells (Panayotides et al. 1986). IL-2 is essential in the early stages of B cell differentiation, and additionally enhances cellular responsiveness to IL-6, a necessary component for late-stage B cell differentiation (Xia et al. 1989).

Conflicting results have been obtained in phenotypic studies of IL-2-activated cells. It appears that results are highly dependent on the concentration of IL-2, the phenotypes of the cell population and the duration of culture. In addition, cell response to IL-2 may be biphasic, with the proportions of cell subtypes altering over a period of days (Winkelstein et al. 1990). This has important implications for IL-2 therapeutic dosage regimens and the methods used to monitor clinical effects, and is described further in section 1.3.1.

1.2.2 Activity Against Tumour Cells

A role for IL-2 in the control of cancer was postulated after IL-2 deficiency was shown to be a factor in tumour growth by Mantovani and colleagues (1986). IL-2 antitumour activity hinges upon the enhancement of natural killer cells, tumour-specific cytotoxic cells, and lymphokine-activated killer (LAK) cells. Effects of IL-2 on tumour cells are

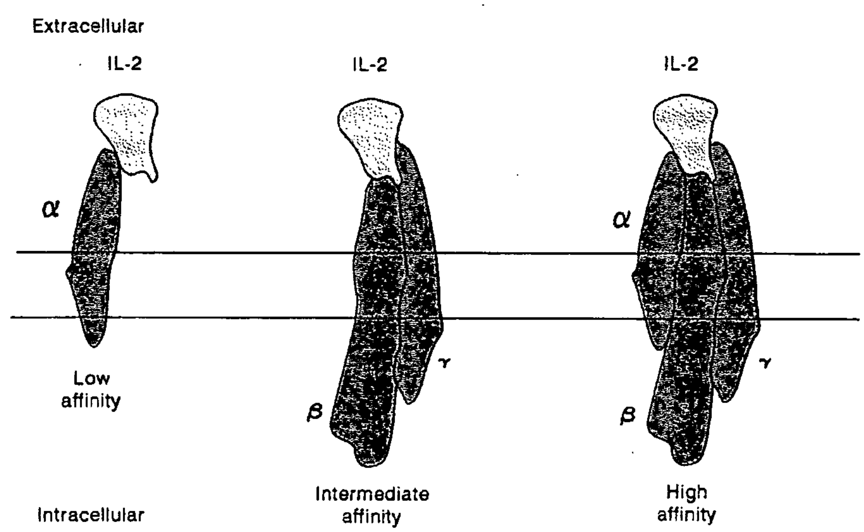

Fig. 2. Schematic representation of interleukin-2 (IL-2) interacting with its low, intermediate and high affinity receptors. Binding to the α (p55) chain occurs first, and signal transduction occurs when IL-2 binds to the β (p75) and γ (p64) chains (after Smith 1993).

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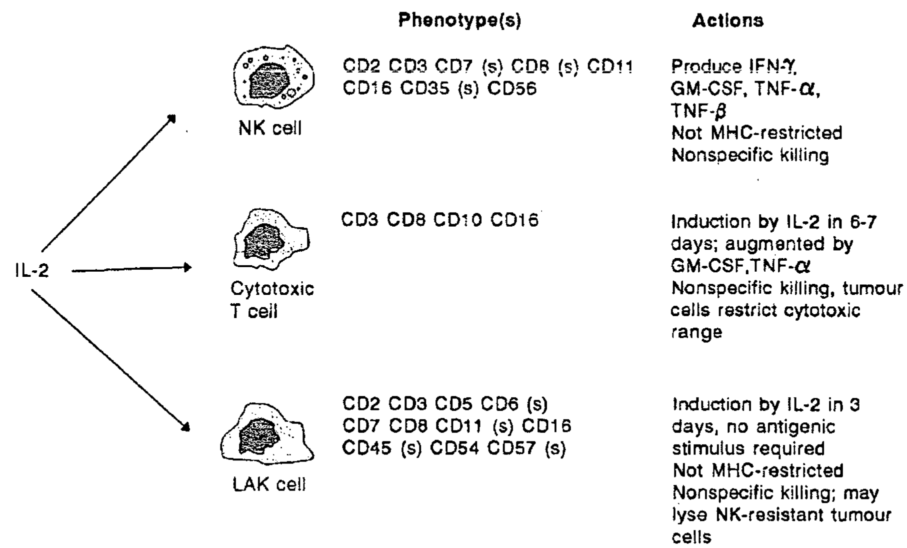

Fig. 3. The probable phenotype and action of cells associated with the antitumour activity induced by interleukin-2 (IL-2). *Abbreviations:* GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; LAK = lymphokine-activated killer; MHC = major histocompatability complex; NK = natural killer; (s) = subset; TNF = tumour necrosis factor.

therefore indirect, and mediated via the immune system: direct effects of IL-2 on tumour cells have not been reported. As mentioned previously, the phenotypes of cells proliferating in response to IL-2 *in vitro* appear to depend on the concentration of IL-2 and the duration of culture. Regional injection of IL-2 *in vivo* may enhance different subsets of lymphocytes, depending on the tumour antigens present (Rivoltini et al. 1990). LAK cell systems are thought to be distinct from cytotoxic T cell or natural killer cell systems, by characteristics that include target cell specificity, kinetics of activation, stimulus requirements, precursor cell location and effector cell phenotype (Grimm et al. 1982, 1983). Established phenotypes and cell subsets are shown in figure 3; however, many authors suggest that cell systems are better differentiated by function than by phenotype, as cell populations do not appear to be entirely discrete (Damle et al. 1986; Ortaldo et al. 1986; Phillips & Lanier 1986; Reynolds & Ortaldo 1987). Antitumour effects appear to be somewhat dependent upon the animal model or tumour cells used, the degree of immunogenicity, and the route of IL-2 administration (reviewed in Winkelhake & Gauny 1990).

Natural Killer Cells

Natural killer cells, together with their *in vitro*-induced LAK cell counterparts, exhibit a broad range of non-MHC-restricted cytotoxic responses. Large granular lymphocytes, thought to be a subset of natural killer cell precursors, respond to IL-2 administration by increased cell proliferation and the production of IFN-γ (Koizumi et al. 1986). These cells comprise 2 to 5% of peripheral blood mononuclear cells, and can be divided into 2 major subtypes. One subtype is characterised by cell surface expression of p222, CD16, CD11b, and Leu-7 antigens. A high percentage of cells express CD2 in the absence of CD3. Cells of the other subtype express high density CD8 and CD3, and are indistinguishable from cytotoxic suppressor cells (Pirruccello et al. 1989). Monocytes suppress the responsiveness of natural killer cells to IL-2, an effect

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that appears to be regulated by histamine (Hellstrand & Hermodsson 1990) and/or prostaglandins (Parhar & Lala 1985).

Activation of natural killer cells by IL-2 induces the multicatalytic proteinase complex, indicating that this complex may have a role in natural killer cytotoxicity (Kitson et al. 1992). Natural killer cells show increased cell rigidity after IL-2 stimulation, which increases when IL-2 is withdrawn from the incubation medium (Melder & Jain 1992).

Cytotoxic Cells

Cytotoxic T cells differ from natural killer cells, as they do not express CD4, CD11 or Leu-7, but express CD3 and CD8 surface antigens as do some LAK cells (Grimm & Rosenberg, 1984). IL-2 induction of cytotoxic cells is augmented *in vitro* by TNF-α (Shalaby et al. 1988) and by granulocyte-macrophage colony-stimulating factor (GM-CSF) [Masucci et al. 1990; Stewart et al. 1992]. This latter action does not appear to be mediated by IFN-γ or IL-1β production (Stewart et al. 1992). It is also unlikely to be due to a positive feedback loop, as IL-2 failed to stimulate production of either GM-CSF or granulocyte colony-stimulating factor (G-CSF) *in vitro*, even in combination with IL-1 (Leizer et al. 1990).

Modulation of adhesion antigens and MHC molecules on melanoma cells appears to influence their susceptibility to IL-2-activated cytotoxic lymphocytes (Roll et al. 1992). Moreover, the presence of autologous tumour cells in the culture has been shown to modify both the degree and range of cytotoxicity of IL-2-activated lymphocytes (Slovin et al. 1990).

IL-2 augments the chemotactic activity of macrophages and T cells (Robbins et al. 1986), via a mechanism involving increased expression of mRNA (Melillo et al. 1992). Macrophages display a rapid (within 5 hours) and direct response to IL-2 *in vitro* and *in vivo* with a marked increase in cytotoxic activity (Maas et al. 1992; Malkovský et al. 1987). IL-2 had no effect on the myeloperoxidase activity of human macrophages *in vitro* (Kakita et al. 1989).

Lymphokine-Activated Killer Activity and Tumour Infiltrating Lymphocytes

As their name suggests, lymphokine-activated killer cells are a functionally defined subset of lymphocytes that have been activated by lymphokines. LAK cells are often non-T, non-B, 'null' lymphocytes capable of killing a wide variety of tumour cells without MHC restriction. Nevertheless, LAK activity can be attributed to numerous cell types, with IL-2 inducing LAK cells from a heterogenous population of lymphoid cells that includes T inducer, T helper/amplifier, T cytotoxic and T suppressor subpopulations (Damle et al. 1986). IL-2-activated LAK cells express CD16 as well as CD3 (Nitta et al. 1991).

In patients, LAK cells are induced *ex vivo* after lymphopheresis, then administered as an adjunct to IL-2 therapy, a procedure commonly termed adoptive immunotherapy. The interaction between IL-2 and LAK cells is complex, and *in vitro* and *in vivo* effects are sometimes dissimilar. For example, cytotoxicity curves indicated that peripheral blood lymphocyte (PBL) activation obtained *in vivo* was 4 to 10 times lower than levels demonstrated *in vitro* with similar IL-2 concentrations, but that the addition of LAK cells to IL-2 therapy increased PBL activation to *in vitro* levels (Gambacorti-Passerini et al. 1989). Differences in effect may also be due to *in vivo* tissue distribution or antigenicity. Whereas LAK cells demonstrated direct cytotoxicity against tumour cells *in vitro*, *in vivo* studies have shown that the majority of infused LAK cells did not localise at tumour sites (Hayakawa 1992). Similarly, Hayakawa (1992) found that while LAK cells accumulated briefly at tumour sites after regional intra-arterial perfusion, systemically-infused LAK cells accumulated in healthy lung tissue. In addition, LAK cells infused into mice were rejected by activated natural killer cells (Brubaker et al. 1991). Antibodies against absorbed antigens of LAK cells and serum inhibitors of IL-2 are generated by repeated challenge *in vivo*, an effect that is absent *in vitro*.

LAK cell activity has been shown to peak at 5 to 10 days in long term culture with IL-2, then to decline significantly. A slow recovery after decline

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has been observed within 3 weeks (Ochoa et al. 1987). Inhibition of LAK cell activity by prostaglandin E_2 (possibly by a mechanism involving cyclic AMP) has been observed in the late phase of IL-2 induction (Eisenthal 1990; Kokudo & Chu 1992; Nakajima & Chu 1990). This effect could be partially overcome by additional IL-2 (Kokudo & Chu 1992) or by indomethacin, a prostaglandin inhibitor (Eisenthal 1990).

A further cell system is now being explored in adoptive immunotherapy – tumour-infiltrating lymphocytes (TIL). When suspensions of the original tumour mass are cultured with IL-2, lymphocyte subsets expand and destroy the tumour cells to yield a pure population of TIL. These cells have increased specific cytolytic activity against their autologous tumours, and require less IL-2 to support their activity than LAK cells. TIL are generally of the CD3 phenotype, and some have been reported to show specific MHC-restricted killing (Baars et al. 1992b). TIL differ from LAK in the following ways: TIL are lymphocytes in the tumour site, whereas LAK cells originate in the blood; TIL contain T, B and natural killer cells, whereas LAK consist of natural killer and some T cells; there is considerable diversity of TIL among histologically distinct cancers, but there is no significant diversity of LAK cells (Itoh 1991). In addition, TIL are more difficult to obtain and culture than LAK cells, as original tumour mass is required.

Although TIL can elicit an effective antitumour response, and are generally considered 50 to 100 times more effective than LAK cells [however some investigators debate this (Nishimura et al. 1991)], tumour regression does not always occur (Koo et al. 1991). When TIL and tumour cells from patients with melanoma were examined after chemotherapy or IL-2 therapy, a decrease in live tumour cells did not always correlate with clinical response. It was also observed that IL-2 therapy may induce a transient unresponsiveness of TIL to IL-2 (Itoh et al. 1991).

TIL phenotype may depend in part on the tumour type and the additives used in the expansion culture. In a pilot study in 4 patients with malignant melanoma, TIL from all patients were predominantly CD8, and infiltration of cutaneous metastases removed after treatment also showed the same CD8 phenotype (Baars et al. 1992b). However, if expansion is induced with IL-2 and anti-CD3 monoclonal antibody, the CD4 subtype becomes the dominant subpopulation (Takayama et al. 1991). TIL isolated from human ovarian tumours, and incubated with IL-2 and TNF-α, show an increased population of CD3/CD8 cells (Vaccarello et al. 1990). Optimum growth conditions appear to be achieved with low concentrations of IL-2 (20 U/ml) in the incubating media, which produce mainly CD3/CD8 cells, with a subset of CD4/CD8 cells. The level of autologous tumour-specific cytotoxicity may correlate with the expression of TNF-α mRNA (Koo et al. 1991).

TIL and LAK recognise their targets by different mechanisms, and lack of response in patients may indicate tumour cell resistance to killing. This may be due to low expression of MHC determinants, or to defects in antigen processing. Alternatively, an absence of tumour-specific cells may preclude a response (Aebersold et al. 1991). Results of a study in which radiolabelled TIL cells were given to patients with hepatic neoplasms, indicated that these cells localised at the tumour sites (Takayama et al. 1991), whereas there is doubt that this occurs with LAK cells.

1.2.3 IL-2 in Combination with Other Cytokines

IL-2 has been studied in combination with a number of agents; however, possibly due to wide variations in effector cell sources, dosages and/or limited numbers of observations, many reports are conflicting. For example, interferons, particularly IFN-α and IFN-β, have been shown to be potent activators of natural killer cell function *in vitro* and *in vivo* (Dieu et al. 1979; Herberman et al. 1982), and could therefore be expected to have additive or synergistic effects with IL-2. Although some studies do report synergistic or additive effects on natural killer cell function with IFN and IL-2 *in vivo* (Chikkala et al. 1990; Iigo et al. 1989; Riccardi et al. 1986) or *in vitro* (Findley et al. 1990; Hinuma et al. 1989), other studies have indicated that the

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administration schedule is important (Fuggetta et al. 1993), and further studies have shown no improvement or a decline in natural killer cell function (Feruglio et al. 1992; Schiller et al. 1993). Similarly, synergistic effects on LAK cells *in vivo* (Puri & Leland 1991; Wanebo et al. 1991) and *in vitro* (Findley et al. 1990) have been reported with IL-2 and IFN in combination, contrasting with other studies reporting a decreased or absent effect (Feruglio et al. 1992). Some (but not all) of the discrepancies may be due to different IFN preparations used in the studies: Kaufmann et al. (1991) showed that IFN-γ had a synergistic effect, whereas IFN-α2, IFN-β1 and IFN-β2 had no influence on IL-2 effects when added to cell cultures. Synergy between IFN-γ and IL-2 may require interaction between IL-2 and its receptor (Delfraissy et al. 1988).

In addition, IFN-γ inhibits the IL-2-induced expression of IL-8 (Musso et al. 1992a). In monocytes, production of IL-6 is stimulated by both IL-1 and IL-2 (Schaafsma et al. 1991), but by independent mechanisms, as IFN-γ inhibits the effect of IL-1 but not IL-2 (Musso et al. 1992b).

Other cytokines are also involved in the activation of cell proliferation and differentiation, by a complex set of interactions (fig. 1). IL-2 and IL-4 appeared to induce T cell proliferation through parallel but independent pathways, with neither agent able to induce inactive T cells (Or et al. 1992). Effects on active or competent T cells were not additive or synergistic, and antibodies to either agent did not interfere with the action of the alternative interleukin. *In vitro*, responsiveness to either interleukin was maintained for approximately 24 hours, then cells became gradually less responsive in the progression phase of the cell cycle (Or et al. 1992). Some investigators have reported both independent and joint stimulatory action of IL-2 and IL-4 on large granular lymphocytes (Bosse & Ades 1991), but other investigators dispute these findings (Blay et al. 1990). IL-4 suppressed IL-2-induced LAK cell development (Ebina et al. 1990; Kawakami et al. 1989) and B cell proliferation (Karray et al. 1988), but induced the proliferation of TIL (Tsunoda et al. 1992). However, findings differ: Tanaka and colleagues (1991) showed that IL-4 enhanced IL-2 production by anti-CD3-stimulated T cells *in vitro*, possibly by enhancing transcription of the IL-2 gene. Experimental conditions may be responsible for these apparent discrepancies.

TNF-α has been shown to augment the cytotoxicity of lymphocytes *in vivo* (Kos 1989) and *in vitro* when cells were coincubated with IL-2 (Herrmann et al. 1989; Ioannides et al. 1992; Matossian-Rogers et al. 1989; Østensen et al. 1989). Dependence of this effect on the administration schedule was shown in 2 murine tumour models (Zimmerman et al. 1989). Relative availability of cytokines was thought to influence the outcome of TNF-α and IL-2 in combination *in vitro*, as TNF-α was found to have a suppressive effect on IL-2-induced cytotoxicity in some cell culture systems (Pawelec 1991). GM-CSF has been reported to augment the induction of LAK cells by low-dose IL-2, independently of both TNF-α and IFN-γ activity (Stewart-Akers et al. 1993).

In summary, it seems evident that the results of *in vitro* studies are very dependent upon experimental conditions, and clear conclusions about the effects of IL-2 either as a sole agent or in combination with other cytokines are at present not feasible. Although *in vitro* data have determined the direction of *in vivo* studies, the presence of circulating cytokines *in vivo* and the large degree of overlap apparent in their actions make comparison with *in vitro* results difficult. Moreover, many studies in animal models indicated synergistic effects of IL-2 in combination with other cytokines *in vivo* that were not shown in subsequent human studies (reviewed in Winkelhake & Gauny 1990). IL-2 activity appears to exhibit species-specific qualities that affect the outcome of the research. In addition, immunogenicity of particular tumour cells may have a major impact on the subsequent effects of IL-2 in culture, and a priority for future *in vitro* work will be to establish the extent of influence of specific antigens present in assay materials.

1.3 Effects in Humans

The pharmacological effects of IL-2 in humans are many and variable (table III), and appear in part to depend on pretreatment patient status.

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Table III. The probable pharmacodynamic effects of IL-2 therapy in patients

Effect	Comment	References
Cellular effects		
↑ Eosinophils	Time course variable, from 2-13 days after initiation of therapy. Possibly due to IL-5	Bertoglio et al. (1989); Creekmore et al. (1989); Huland & Huland (1992); Ishimitsu et al. (1992); Macdonald et al. (1990a); Nakamura et al. (1990); Rosell et al. (1990); van Haelst Pisani et al. (1991)
Early ↓ lymphocytes	Occurs within 1-2 days after initiation of therapy	Fiedler et al. (1992); Laghi Pasini et al. (1992)
Post-treatment ↑ lymphocytes	Occurs usually within 1-2 days of cessation of therapy, with ↑ in % of cells with activation markers	Buter et al. (1992); Caligiuri et al. (1993)
↑ Natural killer cells		Alvarado et al. (1989); Caligiuri et al. (1993); Creekmore et al. (1989); Sondel et al. (1988)
↑ LAK cells	Some investigators doubt this, as LAK cells are difficult to isolate because they marginate and adhere	Albertini et al. (1990); Goldstein et al. (1989); Schomburg et al. (1992)
↓ BFU-E, ↓ CFU-GEMM, ↓ CFU-GM then ↑ after therapy		Gambacorti-Passerini et al. (1992); Schaafsma et al. (1990)
Effects on cytokines		
↑ G-CSF	Peaked after 5 days of therapy	Arienti et al. (1993); Tritarelli et al. (1991)
↑ IFN-γ, TNF-α, TNF-β ?	Data conflicting, may be transient. No correlation with IL-2 dose. LAK infusion may be responsible	Arienti et al. (1993); Becker et al. (1992); Bergmann et al. (1992); Blay et al. (1992a,b); Fortis et al. (1992); Gemlo et al. (1988); Giannella et al. (1989); Jahn et al. (1991); Konrad et al. (1992); Sone et al. (1992)
↔ IFN-α		Jahn et al. (1991); Sone et al. (1992)
↑ IL-1, IL-3, IL-4, IL-5, IL-6		Arienti et al. (1993); Blay et al. (1992a,b); Gemlo et al. (1988); Giannella et al. (1989); Sone et al. (1992) Tritarelli et al. (1991)
Other effects		
↑ Atrial natriuretic factor		Paolorossi et al. (1991)
↑ ACTH, cortisol	Increased response with IL-2 re-treatment	Denicoff et al. (1989); Spinazzé et al. (1991)
↑ β-Endorphin		Denicoff et al. (1989); Spinazzé et al. (1991)
↓ Melatonin		Lissoni et al. (1991a)
↔ GH, LH, FSH, TSH, prolactin		Lissoni et al. (1991a)
↓ Testosterone	Gradually returned to normal with cessation of therapy	Meikle et al. (1991)
↓ Cholesterol	Lowest mean levels after 2 weeks, increased with cessation of therapy	Lissoni et al. (1991b)
↑ Biopterins	Correlated with soluble IL-2 receptor levels	Lissoni et al. (1991c)
↑ Soluble IL-2 receptor	Response may be inhibited with prior chemotherapy; less change observed in patients who respond clinically	Lissoni et al. (1991c)
↑ Soluble CD8 molecule	Possibly correlated with clinical response	Martens et al. (1993)
↑ Soluble ICAM-1	Maximal by day 8 of therapy	Fenchel et al. (1993)
↑ Plasma nitrate	Correlated with ↑ TNF, neopterin, but not with response	Miles et al. (1993)
↑ Histamine release	Effect inhibited by IL-4	White et al. (1992)
↓ Factor XII, prekallikrein		Hack et al. (1991)

Abbreviations and symbols: ACTH = adrenocorticotrophic hormone; BFU-E = burst-forming unit-erythroid; CFU-GEMM = colony-forming unit-granulocyte-erythroid-monocyte-megakaryocyte; CFU-GM = colony-forming unit-granulocyte macrophage; FSH = follicle stimulating hormone; G-CSF = granulocyte colony-stimulating factor; GH = growth hormone; ICAM-1 = cell adhesion molecule; IFN = interferon; IL = interleukin; LAK = lymphokine-activated killer cells; LH = luteinising hormone; TNF = tumour necrosis factor; TSH = thyroid stimulating hormone; ↑ = increase in; ↓ = decrease in; ↔ = no change

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1.3.1 Effects on Haematopoietic Cells

In general, the most frequently observed effects of IL-2 in patients with cancer are eosinophilia, probably due to an increase in eosinophil colony-stimulating factor (IL-5) [Nakamura et al. 1990; van Haelst Pisani et al. 1991], early lymphopenia and rebound lymphocytosis, an increase in natural killer activity and induction of LAK activity, and an augmentation of the percentage of lymphocytes exhibiting activation markers (table III).

IL-2 has a biphasic effect on the number of circulating erythroid (BFU-E; burst-forming unit-erythroid), myeloid (CFU-GM; colony-forming unit-granulocyte-macrophage), and multipotential progenitor cells (CFU-GEMM; colony-forming unit-granulocyte-erythroid-monocyte-megakaryocyte), with a mean decrease during IL-2 infusion of approximately 50%, followed by a mean increase reaching a 20- to 60-fold maximum 5 days after therapy cessation (Schaafsma et al. 1990). Multiple cycles of IL-2 administered by continuous infusion caused a progressive increase in peripheral blood CFU-GM of between 14- and 57-fold by the second or third cycle of treatment (Gambacorti-Passerini et al. 1991).

In patients with lymphoproliferative diseases, a major concern is the possibility of IL-2 resulting in enhanced tumour growth, because the malignant cells may arise from lymphoid cells that are potentially responsive to IL-2. A transient but significant IL-2-induced 8-fold increase in monoclonal B cells has been reported in a patient with lymphocytic lymphoma (Tiberghien et al. 1992).

IL-2 significantly increased the LAK precursor pool after 20 days of therapy (Albertini et al. 1990), and studies have shown that the total number of circulating lymphocytes increased, as well as the percentage of lymphocytes with the natural killer phenotype (Alvarado et al. 1989; Caligiuri et al. 1993; Garritsen et al. 1992; Park et al. 1992; Sondel et al. 1988). Within 10 to 15 minutes of the start of an intravenous infusion of IL-2, however, all natural killer lymphocyte subpopulations disappeared from the peripheral blood of patients. This was thought to be due to increased adherence to activated endothelial cells, induced both by IL-2 alone, and/or combined with the IL-2-induced increase in TNF-α (Salvo et al. 1992). In contrast, cells without natural killer activity remained in the peripheral circulation.

Repeated cycles of IL-2 therapy have been shown to have additive effects on cell proliferation by some investigators (Sondel et al. 1988), but not by others (Eggermont & Sugarbaker 1987). It has been postulated that IL-2-activated cytotoxic T cells and LAK cells may consume IL-2, and thereby inhibit the anti-tumour effects by competitive inhibition (Sugarbaker et al. 1987). This hypothesis is supported by the fact that high doses of IL-2 can restore the anti-tumour effect (Eggermont et al. 1987b). In contrast, Sondel et al. (1988) reported that patients with cancer receiving IL-2 by continuous infusion had greater increases in lymphocyte counts with successive cycles of therapy. Patients received either 3 or 9 × 10^6 IU/m^2/day; and lymphocyte counts dropped sharply within 24 hours of commencement of each cycle. However, it may be that longer infusion periods are required to induce a sustained anti-tumour effect. Low dosage regimens of interleukin-2 have induced a gradual increase in natural killer cell numbers without appreciable expansion of the total CD3 T cell population (Caligiuri et al. 1993). In this study, IL-2 was given continuously for 90 days, at concentrations that selectively saturated high-affinity IL-2 receptors.

1.3.2 Effects on Cytokines

Again, reports of IL-2 effects on other cytokines are conflicting, and it is difficult to determine the precise reasons for discrepancies. Assay methods and dosage regimens may be partly responsible.

Significant increases have been noted in IFN-γ and IL-6 levels after IL-2 therapy (Gemlo et al. 1988; Giannella et al. 1989; Sone et al. 1992). IFN-γ levels rose to a maximum at 4 hours, then slowly decreased, and did not correlate with IL-2 dose (Konrad et al. 1992). Some reports suggested IFN-γ and IL-6 were only detectable for a short period after IL-2 infusion (Jahn et al. 1991; Konrad et al. 1992), although other investigators found that IL-6 peaked after 5 days of treatment with IL-2

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infusion (Tritarelli et al. 1991). IFN-γ has been undetectable in some studies (Schaafsma et al. 1991). Similarly, increases in TNF-α and TNF-β levels have been observed in some studies (Becker et al. 1992; Bergmann et al. 1992; Fortis et al. 1992; Gemlo et al. 1988) and not in others (Miles et al. 1992; Schaafsma et al. 1991; Sone et al. 1992) after IL-2 therapy.

The greatest increases in circulating cytokines (IFN-γ and TNF) have been noted to occur in patients receiving LAK cell infusions, and more frequently in patients having IL-2 by bolus injection compared to continuous infusion (Gemlo et al. 1988). Regional injection of IL-2 into the pleural cavity or cerebrospinal fluid induced cytokine increases within the fluid compartment concerned (List et al. 1992; Sone et al. 1992).

An increase in IFN-α during or after IL-2 therapy was not detected in patients with melanoma or renal cell carcinoma (Jahn et al. 1991; Sone et al. 1992). However, levels of G-CSF peaked at the fifth day of treatment (Tritarelli et al. 1991), and increases in IL-5 and IL-3 mRNA have been noted during IL-2 infusions (Heslop et al. 1991a,b; Schaafsma et al. 1991), as have IL-4 levels (Sone et al. 1992).

1.3.3 Antigenic and Immunological Effects

The generation of antibodies to recombinant products may affect the efficacy and tolerability of the agent and the feasibility of repeated therapy. Differences in immune response to recombinant non-glycosylated IL-2 compared with 'natural', (purified, glycosylated) IL-2 are reported to be minor. Subcutaneous administration of recombinant IL-2 caused the *de novo* production of IgG antibodies in all 14 patients with renal cell carcinoma; whereas natural IL-2 administration produced antibodies in 1 of 5 patients. Although this indicated that recombinant IL-2 has a greater antigenic capacity than the endogenous compound, few patients developed antibodies that were likely to affect the clinical efficacy of IL-2 (Kirchner et al. 1991b; Schwuléra et al. 1992). Preliminary results of a larger study indicate that although antibodies to recombinant IL-2 (aldesleukin) were detected in sera of approximately 50% of 205 patients with metastatic cancer, antibodies that neutralised IL-2 activity were detected only in 15 (7%) patients. Antibodies affected the activity of both recombinant and natural IL-2. Clinical response rates of 16 to 21% were observed in patients in this study; however, it was not stated whether patients with IL-2-neutralising sera achieved clinical responses (Scharenberg et al. 1993).

A further consideration when administering recombinant immunotherapy is to ensure that the patient's immune system is not compromised in the process. Patients developed acute anergy to mitogens and recall antigens during IL-2 continuous infusion with or without LAK cells, becoming refractory to further immune stimulation (Ades et al. 1990a; Kradin et al. 1989a; Wiebke et al. 1988). This rapidly resolved at the cessation of therapy. However, a further study showed that the *in vivo* and *in vitro* responses of patients differed, as patients evincing marked decrease in blastogenic response to antigens or mitogens had normal immunological responses to tetanus booster vaccination (Ades et al. 1990b).

Administration of IL-2 is associated with a modest reduction in total serum immunoglobulin, and a subsequent increased risk of infection. Gottlieb and colleagues (1992) found that patients receiving IL-2 failed to produce any primary antibody response to antigen challenge, and the secondary response was decreased 50-fold compared with control patients. IL-2 appeared to increase the number of circulating unprimed memory cells, but no cells appeared to specifically suppress B cell activity, as the reduction in B cells seen with IL-2 therapy was small and reflected a general reduction in all lymphocytes. Also, removal of cytotoxic (CD8) and natural killer/ LAK cells (CD16) did not restore immunoglobulin secretion. Specific antibody was not detected in patients for up to 7 weeks after the completion of IL-2 therapy, or 8 weeks after antigen vaccination, which indicated that the lack of response was not due to the capillary leak syndrome that often accompanies IL-2 therapy (Gottlieb et al. 1992).

IL-2 may also have the potential to trigger or exacerbate autoimmune reactions, and anti-

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erythrocyte antibodies have been reported in a patient with renal cell carcinoma receiving IL-2 and IFN-γ (Perez et al. 1991). This is substantiated by studies in athymic mice which have indicated that IL-2 may stimulate autoreactive activity from quiescent T cells (Gutierrez-Ramos et al. 1992). Autoimmune thyroiditis has been reported in patients receiving IL-2 and LAK cell therapy (see section 3.6).

1.3.4 Other Effects

Four hours after infusion of IL-2, plasma levels of β-endorphin increased 10-fold, ACTH increased 20-fold and cortisol increased 2-fold in patients with metastatic cancer, with a greater response to re-exposure (Denicoff et al. 1989). Similar responses were seen after subcutaneous injection of IL-2, with significant increases in plasma levels of β-endorphin, cortisol (Spinazzé et al. 1991), marked decreases in melatonin plasma levels, and no significant change in plasma levels of growth hormone, prolactin, follicle stimulating hormone, luteinising hormone or thyroid stimulating hormone (Lissoni et al. 1991a; Meikle et al. 1991). Pretreatment with IL-3 was found to inhibit IL-2-induced cortisol release and neopterin production in patients with lung cancer (Lissoni et al. 1992d, 1993). A rapid decrease was observed in cholesterol levels after IL-2 therapy, with the lowest mean levels seen after 2 weeks (Lissoni et al. 1991b). High dose IL-2 therapy caused a significant decrease in testosterone levels in male patients with malignant melanoma or renal cell carcinoma, reaching a nadir 24 hours after a 5-day course of therapy, then gradually recovering toward baseline levels (Meikle et al. 1991).

IL-2 therapy in patients with cancer caused an increase in total biopterins with or without accompanying infused LAK cells; however, this did not correlate with tumour response (Baker et al. 1989). Neopterin is specifically produced by macrophages, which become activated by IFN-γ produced following IL-2-mediated lymphocyte induction (Boccoli et al. 1990; Brown et al. 1989). Neopterin levels increased to a peak in the second week of subcutaneous IL-2 therapy in patients with renal cancer, which correlated with a rise in soluble IL-2 receptor (Lissoni et al. 1991c) and plasma nitrate levels (Miles et al. 1993). This increase in levels of soluble IL-2 receptor, which is thought to counteract the beneficial effects of therapy, has been inhibited by pretreatment with IL-3 in a small group of 5 patients with advanced lung cancer (Lissoni et al. 1992c). Spiers et al. (1993) observed that the increase in soluble IL-2 receptor reached a plateau with repeated cycles of IL-2 therapy. Serum levels of soluble CD8 (Martens et al. 1993) and cell adhesion molecules (CAM) [Fenchel et al. 1993] have also been noted to rise with IL-2 therapy. Further research is awaited with interest.

IL-2 caused a progressive increase in the levels of atrial natriuretic factor, peaking at 6 hours after subcutaneous injection (Paolorossi et al. 1991). A decrease in factor XII and prekallikrein to 50 and 30% of initial levels, respectively, was observed after 2 cycles of high dose IL-2 therapy, despite correction for possible protein leakage (Hack et al. 1991).

1.4 Pharmacokinetic Properties

IL-2 is thought to act at localised areas of inflammation and immune response, and is therefore not measurable in the systemic circulation under normal physiological conditions. During IL-2 therapy, concentrations of IL-2 are far in excess of those experienced during normal immune system activation. In addition, administration is frequently by intravenous infusion and therefore distribution is potentially throughout the whole body. As a consequence, the pharmacokinetic properties of IL-2 may prove to be of great significance in understanding its antitumour effects. For example, the concentration and antitumour activity of IL-2 may depend in part upon the reconstituting and diluting solution used. Reconstituting IL-2 in human serum albumin increased IL-2-induced TNF-α levels in patients receiving continuous intravenous infusion (Lamers et al. 1992), and may reduce variability in IL-2 serum levels (Bocci et al. 1993; Lamers et al. 1992). Animal studies indicated that albumin also enhanced IL-2 absorption within the lymphatic system, which may reduce toxicity (Bocci et al. 1990). Therefore, a variety of formulations

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and methods of administering IL-2 have been employed in an attempt to increase half-life and the bioavailability to tumour sites, and to reduce toxicity by improved targeting. The effects of these different formulations and modes of administration on the distribution and bioavailability of IL-2 remain largely unresolved.

Radioimmunoassays and enzyme-linked immunoassays are the most commonly used methods to determine IL-2 concentrations (Brandt et al. 1986a,b; Nadeau et al. 1989). These techniques are fairly straightforward when applied to cell culture, but are less reliable when used to measure serum IL-2 concentrations, as substances that block antibody binding, and nonspecific binding molecules are present. Since the amounts of these substances can vary between individuals, direct bioassay is unreliable, with up to 30% intra-assay variability (Levitt 1990). Similarly, assays using levels of mRNA to determine IL-2 production are not feasible as levels can vary *in vitro* by up to a factor of 20 (Gauchat et al. 1986).

Bioassays usually compare proliferation of IL-2-dependent T cell lines incubated with serum samples containing unknown concentrations of IL-2 with standards containing known concentrations of IL-2 (Eskandari et al. 1989; Fleischmann et al. 1989). IL-2-induced killing is frequently measured *ex vivo* by cytolysis of K562 or Daudi target cells.

1.4.1 Distribution

The pharmacokinetic profiles of the various nonglycosylated formulations of IL-2 appear to be similar, although studies have indicated that there is substantial inter-patient and intra-patient variability. Initial studies performed with intravenous IL-2 indicated that the volume of distribution in patients ranged between 6.3 and 7.9L for bolus or 2-hour intravenous infusions (Gustavson et al. 1989; Konrad et al. 1990), and was equivalent to the total calculated extravascular space (reviewed in Winkelhake & Gauny 1990). However, repeated doses of IL-2 appeared to increase the volume of distribution (Sculier et al. 1990).

IL-2 formulated with sodium dodecyl sulphate (SDS-IL-2; e.g. aldesleukin) was distributed in the lungs, liver and kidneys in rodents (Gennuso et al. 1989; Zimmerman et al. 1992), whereas 'Tween 80'-formulated IL-2 was distributed only to the kidneys, after intravenous administration. When SDS-IL-2 was given intraperitoneally in mice it was ineffective against lung metastases, although intravenous doses were effective. Additionally, intravenous SDS-IL-2 was ineffective against subcutaneous tumours in rodents, but peritumoural injections were effective (Zimmerman et al. 1992). These observations suggest that distribution of IL-2 is related to the method of administration, and may affect its efficacy. 38% of a radioactive intravenous dose of IL-2 (formulated with human serum albumin; e.g. teceleukin) was found in the kidneys 5 minutes after administration in rats, suggesting that the kidneys are a major site of clearance. After 1 hour, the majority of radioactivity was located in the carcass (46%) and skin (15%) [Sabo et al. 1992]. In mice, however, IL-2 (formulated with bovine serum albumin) rapidly accumulated in the kidney, liver and spleen within the first 15 minutes after intravenous injection, whereas intraperitoneal doses were distributed nonspecifically (Sands & Loveless 1989).

1.4.2 Plasma Concentrations and Elimination

After intravenous bolus administration to patients, aldesleukin concentration initially decreased with a half-life of 13 minutes, followed by a slower phase with a half-life of 85 minutes to 4 hours (Konrad et al. 1990; Sarna et al. 1989). A 1-hour aldesleukin infusion showed similar biphasic characteristics, with half-lives of 6 to 27 minutes, and 1.5 to 12 hours for the first (α) and second (β) phases, respectively (Weidmann et al. 1992). Teceleukin had a mean half-life after intravenous infusion of 40 to 104 minutes, with a mean clearance of 3 to 11 L/h (Gustavson et al. 1989). Serum concentrations were linearly proportional to dose, but no significant correlation between the dose and the half-life (aldesleukin; Konrad et al. 1990) or AUC (area under the plasma concentration-time curve) after subcutaneous injection (teceleukin; Gustavson et al. 1989) was seen. Subcutaneous administration of IL-2 (aldesleukin) with or without 20%

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human plasma albumin in 13 patients with cancer, indicated that plasma concentrations of IL-2 are slightly higher and sustained for longer when IL-2 is administered with albumin. AUC differences, however, were not statistically significant (Bocci et al. 1993). Clearance rate for aldesleukin was approximately 7.2 to 16.1 L/h, consistent with the major route of clearance being via the kidney (Anon. 1992a; Konrad et al. 1990). Animal studies suggest that IL-2 is metabolised by the renal tubules, as minimal levels of active IL-2 are found in the urine (Donohue & Rosenberg 1983).

During a 24-hour intravenous infusion serum IL-2 concentrations appeared to reach steady-state at the 6-hour measurement with teceleukin (Gustavson et al. 1989), and at 2 hours with aldesleukin (Konrad et al. 1990). Neither study extended beyond 24 hours. However, steady-state serum IL-2 concentrations may not be obtainable with longer continuous intravenous infusions, perhaps due to IL-2-induced increases in IL-2 receptors. Aldesleukin 18×10^6 IU/m^2/day (1.1 mg/m^2/day) administered as a continuous intravenous infusion to 12 patients with either metastatic renal cell carcinoma or melanoma, resulted in maximum serum IL-2 concentrations of 40 IU/L (2.2 $\pm$ 1.1 μg/L) after 24 or 48 hours. Thereafter, serum IL-2 concentrations declined to 10.6 IU/L (0.59 $\pm$ 0.43 μg/L) by the end of the 5-day treatment period. $AUC_{(0-5d)}$ ranged from 48 to 260 IU/day/ml (2.7 to 14.5 μg/day/L) [Fish et al. 1991].

The pharmacokinetic properties of subcutaneous, intraperitoneal, and intramuscular aldesleukin have been explored in preliminary studies in patients. Subcutaneous bolus injection of aldesleukin 9 and 1.8×10^6 IU/m^2 resulted in peak serum concentrations of 40, and 4.5 to 5.5 IU/ml, respectively, after 2 to 3 hours in 3 patients with renal cell carcinoma or melanoma. The higher dose was given to patients already receiving IL-2 therapy, with measurements made after at least 2 days. Thus, smaller doses may maintain plasma IL-2 concentrations despite plasma concentrations being undetectable 12 hours post-injection (De Lena et al. 1992). Serum IL-2 concentrations remained fairly constant for about 8 hours after subcutaneous or intramuscular injection, but were approximately 2% of those observed immediately after intravenous bolus (Konrad et al. 1990).

Intraperitoneal injection of IL-2 1.5×10^6 IU/kg in 8 patients with intra-abdominal cancer resulted in mean peak serum concentrations of 20 to 40 U/ml over an 8-hour period, approximately 100 times lower than mean peak intraperitoneal concentrations. Peak serum concentrations were observed approximately 30 minutes post dose, and were more stable than intraperitoneal fluid concentrations which fluctuated by 50 to 60% with subsequent doses. Concentrations of IL-2 decreased by approximately 70% after 8 hours, but increased to higher peak concentrations with subsequent doses than were seen with the initial dose. The second cycle of therapy caused still higher peak IL-2 concentrations (Urba et al. 1989). Pharmacokinetic studies in patients with ovarian cancer suggested that peak serum IL-2 concentrations occurred within 3 to 6 hours after intraperitoneal injection, and correlated closely with intraperitoneal fluid concentrations as shown by the AUC, but were again approximately 100 times lower, concurring with the results of Urba et al. (1989) [Stewart et al. 1990].

Following injection into the cerebrospinal fluid (CSF) of patients with metastatic brain tumours, IL-2 appeared to have a longer half-life than that seen in peripheral blood. CSF IL-2 concentrations gradually decreased over 24 hours with a half-life of 4 to 8 hours (List et al. 1992).

A 15-minute infusion of aldesleukin administered to patients aged 6 to 18 years had a similar pharmacokinetic profile to that in adult patients, with data fitting a 2-compartment model. A mean half-life of 14 $\pm$ 6 minutes, with a second half-life of 51 $\pm$ 11 minutes was observed, indicating a rapid distribution phase followed by a slower elimination phase. The volume of distribution approximated total extracellular fluid (Pais et al. 1990).

PEG-IL-2 has a substantially prolonged half-life with a corresponding decrease in clearance, and has a pharmacokinetic profile that appears to be independent of dose (Meyers et al. 1991). Other formulations of IL-2, including liposome encap-

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sulation (Anderson et al. 1992; Gause et al. 1993; Silver et al. 1991), and IL-2 linked to a gel matrix, pellets or beads (Crum & Kaplan 1991; Fujiwara et al. 1990; Johnston et al. 1992) are being investigated, but pharmacokinetic data are not yet available.

2. Therapeutic Use of IL-2

There are several problems inherent in both undertaking and interpreting the results of clinical trials using IL-2. Firstly, there is often no generally accepted standard treatment for these conditions against which IL-2 effectiveness may be measured, and placebo-controlled trials are inappropriate in this group of patients, thereby making direct comparisons of treatment protocols difficult. Secondly, patients tend to undergo a variety of treatments before receiving IL-2, which itself is usually part of a treatment continuum. Thus, the value of comparisons between patients within a trial and between trials is limited. Furthermore, IL-2 is used in many different dosage regimens and protocols; at present there is no general agreement on the optimum dosage or route of administration. This also hinders comparison between trials. Dose withholding is common due to the adverse effects experienced with the drug (section 3), making dosage evaluation very complex. Nevertheless, a large number of trials have been successfully performed in patients with cancer, and a broad review of the results to date is presented here. At present, it seems that most European clinicians now favour the subcutaneous route of administration, while US clinicians tend to use either subcutaneous or continuous intravenous delivery of IL-2 (personal communication, Dr CR Franks, EuroCetus). These protocols have not yet been approved in either setting by the appropriate authorities; the approved schedules are intravenous bolus in the US, and continuous infusion in Europe.

This review focuses on the use of IL-2 in patients with renal cell carcinoma, malignant melanoma, colorectal, bladder and ovarian cancer, non–Hodgkin's lymphoma and acute myeloid leukaemia. Many studies included patients with a range of different neoplasms; however, only patients with the indications listed above have been considered when trial results are evaluated. Similarly, tables comparing results of different trials and the calculation of response rates have also included only patients with these diagnoses. In some instances, where patient numbers are limited, this may mean that a trial has been excluded from consideration. Nevertheless, it is the opinion of the authors that the trials discussed herein are representative of the bulk of published work to date.

Response to therapy is determined by the same criteria in most trials. The objective response rate is the most frequently reported parameter and is defined as the sum of complete and partial response rates. Complete response is defined as the complete resolution of all clinical evidence of tumour, sustained for at least 2 measurements separated by a minimum of 4 weeks. Partial response is defined as a ≥50% reduction in all measurable tumours, usually determined by the sum of the cross-sectional diameters. No simultaneous increases of tumour or appearance of new tumour are acceptable. A minor response is determined by a 25% to 49% reduction in the sum of all measured lesions for a minimum of 4 weeks. The criteria for stable disease is <25% decrease or increase in tumour size for at least 3 months. Progressive disease (PD) is termed a ≥25% increase in the sum of all measured lesions, or the appearance of new lesions. More recently, emphasis has shifted towards survival duration rather than response rate or duration, as a more suitable measure of treatment efficacy. Results from a small trial in patients with renal cell carcinoma indicated that immunotherapy may increase survival in both responding and nonresponding patients (Schoof et al. 1993). Unfortunately, most published studies do not include survival data.

The clinical outcome of therapy is influenced by the number of organs involved and the pattern of metastases. Some patients have a 'mixed response' to immunotherapy, with some tumours shrinking while others grow, despite synchronous location in bilateral organs. This suggests that tumours within the same patient may be antigenically different, and

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therefore do not respond equally to the same therapy (Logan et al. 1992). Patients with metastatic lesions in 1 or 2 different organ sites are more likely to achieve partial response or complete response with combination therapy than patients with 3 or more organs involved (Kirchner et al. 1991a). However, there does not appear to be any correlation between response and disease bulk or site of metastases (Lipton et al. 1993; Rosenberg et al. 1989), although some investigators dispute this. In some studies, patients with pulmonary and soft tissue metastases appear more likely to respond than patients with liver, brain or bony metastases, or with unresected abdominal disease (Atkins et al. 1993b; Fisher et al. 1988). Patient selection procedures may partially account for these conflicting data. Multivariate analyses of 327 patients indicated that the number of metastatic sites (1 *vs* ≥2) was also an important predictor of survival (Palmer et al. 1992b).

It appears that patients who relapse after IL-2 therapy do so equally at pre-existing and new sites of disease. There appears to be no difference in recurrence rates between patients who previously achieved complete or partial response. However, response to further IL-2 therapy is less likely in patients with melanoma or renal cell carcinoma, although some patients have responded (Rosenberg et al. 1988). Responses to further IL-2 therapy may be possible in patients with acute myeloid leukaemia or non-Hodgkins lymphoma (Sherry et al. 1991; Weber et al. 1992; see sections 2.8, 2.9).

IL-2 has been administered in several large multicentre trials in both the US and Europe, and clinical trials can generally be classified according to the dosage regimen being high (e.g. $\geq 3 \times 10^5$ IU/kg/day given as an intravenous bolus 3 times per day) or intermediate/low intensity (e.g. $\leq 18 \times 10^6$ IU/m^2/day by continuous infusion). However, the relationship between dosage and response is unclear. There is some doubt whether immunotherapy exhibits dose-dependent efficacy (Budd et al. 1992), and although many earlier trials were concerned with establishing the maximum tolerated dosages of IL-2, later research is directed towards establishing the optimum enhancement of parameters that may correlate with clinical response. Some studies have indicated that cumulative dose is important, with patients receiving the highest total amount of IL-2 being more likely to respond (Hermann et al. 1991). This is frequently difficult to assess when comparing trial reports, and no attempt has been made to reach definitive conclusions on this issue in the review.

2.1 Markers of Clinical Response

Much research has been directed towards identifying clinical markers that may predict or monitor antitumour effects. Nevertheless, the difficulties in interpreting results of clinical trials (section 2) and the heterogeneous patient population again make definitive conclusions untenable. Changes in lymphocyte counts do not appear to correlate with clinical response (Palmer et al. 1992a; Redman et al. 1991; Rosenberg et al. 1993). However, other studies have found that changes in cell populations are in part related to treatment efficacy (Arinaga et al. 1992; Banerjee et al. 1991; Harel et al. 1990; von Rohr et al. 1993; Wersäll et al. 1992; West et al. 1987).

Patients who responded showed a greater increase in the number of IL-2 receptor-bearing (Tac-bearing; CD25) lymphocytes after 1 to 3 cycles of IL-2 than those who did not (Banerjee et al. 1991; Isacson et al. 1992; Keilholz et al. 1992a; Wersäll et al. 1992). Alternatively, the density of CD56 (Leu 19) on natural killer cells may be a more reliable clinical marker, as investigators have observed concentrations >2-fold higher in responding patients before and after treatment with subcutaneous IL-2 than in nonresponders (Duensing et al. 1992; Hänninen et al. 1991).

Patient medical history may also influence treatment outcome. For example, previous chemotherapy may blunt the biological response to IL-2 treatment, as patients who had not undergone prior chemotherapy had significantly higher IL-2 receptor expression after 4 weeks of IL-2 therapy than patients who had received chemotherapeutic pretreatment (Atzpodien et al. 1991b). Another factor may be the timing of the measurement of the

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clinical marker. Patients with renal cell carcinoma who responded to IL-2 plus indomethacin therapy showed a transient significant increase in absolute CD3, CD4, CD8, CD56 and CD3/CD25 T lymphocyte populations after the initial phase of treatment, compared with nonresponders. After the second and third treatment phase, the difference persisted only for CD56 cells, and by the end of treatment the numbers of cells carrying the IL-2 receptor (CD25) had decreased in the responding patients relative to nonresponders (Banerjee et al. 1991). Similar trends were seen in patients receiving IL-2 in combination with IFN-α (Schneekloth et al. 1993; von Rohr et al. 1993). However, no differences were noted between responding and nonresponding patients with malignant melanoma receiving the same treatment regimen (Banerjee et al. 1991). Biopsies of malignant epidermal tumours from 2 patients showed that IL-2 therapy induced redifferentiation of tumour cells, rather than causing cell death (Mihara et al. 1990). Redifferentiation has also been described in bone tumours (Sato et al. 1990).

In 13 patients with malignant melanoma receiving sequential dacarbazine, cisplatin and IL-2, increased LAK cell activity correlated with increased CD56 cell numbers, but none of the changes in lymphocytes correlated with clinical response (Redman et al. 1991). However, patients with renal cell carcinoma receiving combination therapy with cyclophosphamide, IFN-α and IL-2, who responded to therapy, showed significant increases in CD3-/CD56 cells, changes in CD3/CD56- cells, and decreases in CD45R, CD11c and CD54 cells (Wersäll et al. 1992). Soluble CD8 protein levels were significantly higher in the serum of responding patients with renal cell carcinoma, who received IL-2 therapy subcutaneously. Levels of soluble CD8 protein in the initial stages of therapy showed a 2.7- to 3.5-fold increase in responding patients, compared to a 1.4- to 2-fold increase in nonresponding patients (Martens et al. 1993). Other investigators have not detected links between response and phenotypic modifications to lymphocytes (Favrot et al. 1990).

Plasma levels of cytokines may be prognostic for clinical response, but again, results to date have been conflicting. Responders to IL-2 therapy with or without IFN-α were observed to have significantly higher levels of IL-1 and TNF 48 hours after cessation of therapy than were nonresponders (Blay et al. 1992b). In contrast, other investigators found no direct correlation between the levels of TNF-α, IFN-γ, or IL-1α and clinical response in patients with malignant melanoma or renal cell carcinoma (Hänninen et al. 1991; Isacson et al. 1992; McIntyre et al. 1992).

Pretreatment levels of C-reactive protein were lower in responding than nonresponding patients with colorectal carcinoma (Broom et al. 1992; Simpson et al. 1992) and in patients with renal cancer (Blay et al. 1992a); however, levels of C-reactive protein increased substantially with IL-2 treatment in responders, while levels in non-responders remained the same (Broom et al. 1992). Blay et al. (1992a) observed that C-reactive protein levels correlated with levels of IL-6, and that higher levels were linked with poorer prognosis and decreased survival duration. Higher pretreatment levels of α-1-antitrypsin, and lower levels of retinol binding protein and transferrin have also been correlated with failure to respond (Simpson et al. 1992).

Responsiveness to IL-2 therapy may depend in part on the HLA type of the patient. In one study, the haplotypes of patients with malignant melanoma or renal cell carcinoma who responded to therapy were compared with those of patients who did not. 14 responding patients (of 24; 58% of the group) carried one or more of HLA-A2, HLA-B44, and HLA-DR4 alleles, compared with 1 responding patient (of 11; 9% of this group) who lacked these alleles (Scheibenbogen et al. 1992b). Haplotypes were determined in 32 patients with melanoma, including 16 responders, and the frequency of alleles was compared in 76 patients with malignant melanoma and 126 blood donors. All 3 alleles were increased in responders. HLA-B44 was present in 44% of responders, 14.9% of melanoma controls, and 13% of blood donors; HLA-Cw7 was present in 62.5% of responders, 33% of control patients with melanoma and 48% of blood donors,

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and there was also a slightly increased prevalence of HLA-A2 in responders (Scheibenbogen et al. 1992a). Other investigators have found that HLA-DR3 correlated with nonresponse, whereas higher levels of HLA-DR1 and HLA-DQ correlated with response rate in patients with metastatic melanoma (Rubin et al. 1992). However, as patient numbers were very small, and patients were receiving many varieties of IL-2-based therapy, more studies are required to confirm these findings.

Another study indicated that the A11 phenotype was not only associated with melanoma, but also with patients responding to various therapies, particularly TIL. These authors suggested that some HLA class I specificities may predict response to IL-2-based therapy, whereas HLA class II phenotypes correlated with tolerance to the combination of TIL and IL-2 (Marincola et al. 1992). Janssen et al. (1992) have found that high lymphocyte numbers and high numbers of cells that express the HLA-DR activation marker are prognostic of a good therapeutic response. In this study of 27 patients with metastatic renal cell carcinoma, the 2 patients who achieved complete remissions after subcutaneous IL-2 had considerably higher numbers of $CD8^{bright}$ and CD56 cells that expressed HLA-DR. These preliminary reports indicate significant promise for future improvement of patient selection for IL-2 therapy.

It has been suggested that the expression of activated *ras* oncogene may be associated with the susceptibility of melanoma tumours to the lytic action of activated lymphocytes, as the frequency of response to IL-2 therapy is similar to the frequency of occurrence of the *ras* oncogenes within these patients (Parmiani et al. 1992). However, evidence to support this is in murine tumours only, and no further studies have been reported in humans to date.

Expression of the IL-2 receptor p55 gene is very variable during IL-2 therapy, and does not appear to be linked to patient response (Hayat et al. 1992).

Some controversy has been raised as to whether IL-2 is useful in therapy, or whether the clinical responses seen are due to concomitant therapy being given to ameliorate toxicity. Mertens et al. (1992) have suggested that, as the clinical response in some of their patients began to manifest before the initiation of IL-2 therapy, clinical response may in fact be due to indomethacin and ranitidine in combination, rather than the cytokine. As mentioned previously (section 1.2.2), indomethacin augments the induction of LAK cells by inhibiting prostaglandin synthesis (Eisenthal 1990). This provocative hypothesis requires more supporting data before it becomes generally acceptable.

2.2 Adoptive Immunotherapy

Adoptive immunotherapy, using either LAK cells or TIL, is frequently given in conjunction with IL-2 therapy. The *ex vivo* induction of LAK cells has already been discussed (section 1.2.2), and many trials have included LAK cell adoptive immunotherapy in an attempt to improve the effectiveness of IL-2 treatment. Preclinical and early clinical studies with LAK therapy were promising, as LAK coadministration elicited a greater response than IL-2 alone (Lafreniere & Rosenberg 1985; Papa et al. 1986; Rosenberg 1989). IL-2-induced LAK cells may also have a therapeutic effect without the administration of direct IL-2 therapy. In a pilot study where patients with cancer received rapidly-induced LAK cells without IL-2 direct therapy, 6 of 19 patients (31%) achieved partial responses (Yeung et al. 1993).

A trend towards increased survival was noted in patients with melanoma who were given LAK cells in combination with IL-2 therapy, compared to those who received IL-2 alone. This trend was not evident in patients with renal cell carcinoma, who participated in the same randomised trial (Rosenberg et al. 1993). Similarly, a series of 5 trials indicated there was no significant difference in dosage or tumour response in patients with renal cell carcinoma receiving IL-2 with or without LAK cells, and LAK cell administration was correlated with significantly higher toxicity (Palmer et al. 1992a). Preliminary results of other randomised trials in patients with malignant melanoma or renal cell carcinoma have not shown significant differences in response rates with or without LAK cell

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Table IV. Summary of trials in ≥20 patients[a] with advanced renal cell carcinoma receiving interleukin-2 with or without adoptive immunotherapy

Reference	No. of evaluable patients	Interleukin-2 regimen (x 10^6 IU/m²/d)[b]	Period between cycles (weeks)	Adoptive immunotherapy	Response (% of patients)[c] objective	complete	partial	Comment
Atkins et al. (1993b)[d]	71	72 IVb, q8h d1-5, 15-19			17	6	11	Overall median survival 15.5mo
Bukowski et al. (1993)	41	60 IVb 3x per week q4w			12	2	10	
	33	1-4.5 IVc d1-5, 8-12, 15-19		TIL	9	0	0	No prior systemic treatment
Davis et al. (1990); Wang et al. (1989)	43	1.8-3 x 10^5 IU/kg/d IVc d1-5	3	LAK	39	3	36	x-Ray evaluation of tumours, maintenance therapy with IFN-α
Dillman et al. (1993)	46	18 IVc d1-5, 11-15	3-4	LAK	15			Median survival 8.5mo. Response duration 1->24mo
Douillard et al. (1991)	57	20 IVc d1-5, 15-18, 29-31			21	4	17	
Escudier et al. (1992)	68	24 IVc d1,2 q5w			18	0	18	33% SD
Fisher et al. (1988)	32	6 x 10^5 IU/kg IVb q8h d1-5, 12-16	12	LAK	16	6	9	
Gaynor et al. (1990) NC-L287-69 (Multicenter USA)	25	18 IVc d 1-4.5 (ind) then 18-27 IVc d11-16	10	LAK	16	8	8	Response duration 7->13mo
Geertsen et al. (1992)	30	18 IVc d1-5, 12-16.5	3		20	7	13	Overall median survival 261d
Hermann et al. (1991)	26	18 IVc d1-5, 12-16			23	8	15	Cumulative dose correlated with response
Lopez et al. (1993)	27	18 IVc d1-5, 10-15, 20-25	2-4		15	4	11	33% SD. Response duration >3->29mo
McCabe et al. (1991)	37	6 x 10^5 IU/kg q8h IVb d1-5, 11-15			8	3	5	Response duration 5, >10, 20mo. No significant differences ± LAK
	30	6 x 10^5 IU/kg q8h IVb d1-5, 11-15		LAK	13	0	13	Response durations >1->28mo
Négrier et al. (1989) EC-L2-015, EC-L2-008	42	18 IVc d1-5, 11-14.5	3-4		28	10	18	No significant differences ± LAK
	51	18 IVc d1-5, 11-14.5	3-4	LAK	19	6	12	
Négrier et al. (1992)†	22	18 IVc d1-5, 11-15	3		14	9	4	No systemic pretreatment

Table IV. Contd

Reference	No. of evaluable patients
Parkinson et al. (1990b)	47
Rosenberg et al. (1989)	58
	74
Rosenberg et al. (1993)	41[f]
	46[f]
Slaijfer et al. (1992)†	26
Sorio et al. (1991)	20
Thompson et al. (1992)	a) 20
	b) 22
von der Maase et al. (1991)	51
Weiss et al. (1992)	a) 46
	b) 48
Whitehead et al. (1993)	44

a Majority of patients had
b Unless otherwise stated
c Objective response = s
response = disappearan
d Results from one arm o
e Information from Rosen
f Some of these patients
Abbreviations and symbols:
min; IVc = continuous intra
in measurable tumour; NS
disease; TIL = tumour infilt

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eukin-2 with or without adoptive

)[c] partial	Comment
11	Overall median survival 15.5mo
10	
0	No prior systemic treatment
36	x-Ray evaluation of tumours, maintenance therapy with IFN-α Median survival 8.5mo. Response duration 1->24mo
17	
18	33% SD
9	
8	Response duration 7->13mo
13	Overall median survival 261d
15	Cumulative dose correlated with response
11	33% SD. Response duration >3->29mo
5	Response duration 5, >10, 20mo. No significant differences ± LAK
13	Response durations >1->28mo
18	No significant differences ± LAK
12	
4	No systemic pretreatment

Table IV. Contd

Reference	No. of evaluable patients	Interleukin-2 regimen (x 10^6 IU/m^2/d)[b]	Period between cycles (weeks)	Adoptive immuno-therapy	Response (% of patients)[c]			Comment
					objective	complete	partial	
Parkinson et al. (1990b)	47	6 x 10^5 IU/kg q8h IVb d1-3 (ind), then 18 IVc d9-15	12	LAK	9	4	4	Response duration 8->15mo
Rosenberg et al. (1989)	58	7.2[e] x 10^5 IU/kg q8h IVb d1-5, 14-18			22	7	15	
	74	7.2[e] x 10^5 IU/kg q8h IVb d1-5, 14-18		LAK	35	11	24	
Rosenberg et al. (1993)	41[f]	7.2 x 10^5 IU/kg q8h IVb d1-5, 11-15			24	10	14	Response duration 19->61mo
	46[f]	7.2 x 10^5 IU/kg q8h IVb d1-5, 11-15		LAK	33	15	18	Response duration 3->62mo
Sleijfer et al. (1992)†	26	18 x 10^6 IU/d SC d1-5 (ind) then 9 x 10^6 IU/d SC d1,2, 18 x 10^6 IU/d SC d3-5 q5w	3		23	8	15	50% SD. 1 patient had previous systemic therapy
Sorio et al. (1991)	20	18 IVc d1-5, 8-13	3		25	20	5	5% MR, 15% SD
Thompson et al. (1992)	a) 20 b) 22	a) 6 IVc d1-5, 12-16 b) 6 IVc d1-5, then 2 IVc d10-20		LAK	a) 25 b) 41	a) 10 b) 9	a) 15 b) 32	a) CR >18->36mo; b) CR >5->14mo
von der Maase et al. (1991)	51	18 IVc d1-5, 12-15,	3		16	4	12	
Weiss et al. (1992)	a) 46 b) 48	a) 6 x 10^5 IU/kg q8h IVb d1-5, 11-15 b) 18 IVc d1-5, then 22.5 IVc d11-15		LAK	a) 20 b) 14	a) 13 b) 4	a) 13 b) 10	a vs b NS
Whitehead et al. (1993)	44	3-6 IVc d1-4, q4w	2-3		9	0	9	18% SD. Overall median survival 13mo

a Majority of patients had undergone previous nephrectomy, and approximately 50% had received previous radio- chemo- or immunotherapy.†
b Unless otherwise stated.
c Objective response = sum of complete and partial responses; complete response = disappearance of all measurable tumour; partial response = disappearance of $\geq$ 50% of all measurable tumour.
d Results from one arm of a randomised trial. Remainder of data shown in table V.
e Information from Rosenberg et al. (1993) suggests that IL-2 dosages are 7.2 x 10^5 IU/kg and not 6 x 10^5 IU as stated in the original report.
f Some of these patients may be included in the data from Rosenberg et al. (1989).
Abbreviations and symbols: CR = complete response; d = day; IFN-α = interferon-alpha; ind = induction phase; IVb = intravenous bolus $\leq$15 min; IVc = continuous intravenous infusion; LAK = lymphokine-activated killer cells; mo = months; MR = minor response, $\geq$ 25% reduction in measurable tumour; NS = not statistically significant; q8h = every 8 hours; qnw = for n weeks; SC = subcutaneous injection; SD = stable disease; TIL = tumour infiltrating lymphocytes; † = trials in patients who had no previous systemic therapy.

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therapy, but survival data are lacking (McCabe et al. 1991).

More recently, TIL have been used in conjunction with IL-2 therapy. TIL from melanoma patients caused preferential cytolysis of autologous tumour cells, with greater activity in patients responding clinically. This association between activity and clinical response was not observed in patients receiving IL-2 and LAK cells (Rivoltini et al. 1992). However, the clinical response rate in subsequent trials has not sustained this promising beginning. A 9% response rate was observed in 33 patients with renal cell carcinoma who had no treatments prior to receiving IL2 and TIL therapy (Bukowski et al. 1993). In another trial, patients with metastatic melanoma who failed to respond to IL-2 showed no response to subsequently given TIL therapy (Dorval et al. 1992).

In summary, it is evident that adoptive immunotherapy has not been as effective as might be expected. It is very difficult to determine the extent of the influence of adoptive immunotherapy on IL-2 treatment, as IL-2 may be causing similar effects on patients *in vivo* as it does on the patients' cells in culture. Because there is some doubt whether adoptive immunotherapy significantly enhances IL-2 treatment, trials with or without adoptive immunotherapy have been evaluated together in this review. Osterwalder (1992) provides a detailed discussion of the merits of IL-2 treatment ± adoptive immunotherapy, and concludes that adoptive immunotherapy at present appears to offer no significant advantages to patients.

2.3 Renal Cell Carcinoma

Renal cell carcinoma is the most common malignancy of the kidney, and accounts for almost 3% of all adult cancers. Surgery results in cure in approximately 50% of patients with disease confined to the kidney. However, patients with advanced (metastatic) renal cell carcinoma have a poor prognosis, with a median survival after the diagnosis of metastases of approximately 8 months (Maldazys & deKernion 1986). There is currently no standard therapy for patients with metastatic renal cell carcinoma. Chemotherapy, hormonal therapy, angioinfarction, IFN-α, embolisation, immune RNA and debulking surgery have all been attempted, with results that are discouraging in rate or duration of response, or reproducibility. Spontaneous regression is documented in fewer than 1% of patients, and so immunotherapy offers clear advantages to patients with metastatic renal cell carcinoma.

In general, the response rate with conventional cytostatic agents or hormonal therapy is <10% to 15% (reviewed in Stahl et al. 1992). IFN-α was the first immunotherapeutic agent used to treat patients with renal cell carcinoma, and has demonstrated objective response rates of approximately 15 to 20% (reviewed in Choudhury et al. 1993). Whereas IFN-α affects tumour cells directly as well as demonstrating immunomodulatory effects, IL-2 appears to have no direct effect on solid tumour cells, and is thought to exert its antitumour effects indirectly. Nevertheless, with marginally higher response rates IL-2 therapy appears to offer therapeutic advantage over IFN-α monotherapy in patients with renal cell carcinoma (reviewed in Stahl et al. 1992). In addition, many of the clinical responses achieved with IL-2 are more durable than those achieved with IFN-α, with a few patients remaining in remission for >66 months after IL-2 therapy (Rosenberg et al. 1993).

Table IV summarises data from trials of IL-2 with or without adoptive immunotherapy involving ≥20 patients evaluable for response. The majority of patients had nephrectomy and previous systemic chemo-, radio- or biotherapy before commencing IL-2 therapy; however, three trials in patients with no prior systemic therapy showed similar objective response rates to other trials (Bukowski et al. 1993; Négrier et al. 1992; Sleijfer et al. 1992; see table IV). The objective response rate was approximately 20%, ranging from 0 to 40% if trials that included less than 20 patients are also considered (Foon et al. 1992; Koretz et al. 1991; Thompson et al. 1992; Vlasveld et al. 1992; Whitehead et al. 1990). A preliminary trial using PEG-IL-2 in 35 patients yielded an objective response rate of 6% (Bukowski et al. 1993).

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Chemotherapy, hormonal
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led an objective response
al. 1993).

Survival of patients varies considerably; however, many studies have shown little survival advantage for those who do not achieve an objective response. In the largest studies partial responses have lasted for 1 to >53 months before relapse, and complete responses have persisted for 6 to >62 months (Rosenberg et al. 1993); notwithstanding, the median response duration was often ≤10 months (Dillman et al. 1993; Palmer et al. 1992a; Parkinson et al. 1990a). In contrast, Atkins and colleagues (1993b) reported that median survival was 15.5 months in 71 patients receiving high dose IL-2 therapy, and that responses were very durable: 10 of 12 responding patients achieved ongoing responses of >12 to >26 months' duration. Multivariate analyses of results from patients with metastatic renal cell carcinoma who received IL-2 in a series of five trials (excluding patients with brain metastases), indicated that three factors were important predictors of reduced survival time: an ECOG performance status of 1 *vs* 0; a time from diagnosis to trial entry >24 months; and 2 or more metastatic sites, with lung, bone and 'other' considered as single sites. Patients with 3 risk factors had a median survival of 5 months, compared with 28 months for patients with no risk factors (Palmer et al. 1992b). However, Schoof et al. (1993) compared the actual survival of 12 patients with renal cell carcinoma who received IL-2 plus LAK cell therapy, with their projected survival based on their risk factors present at trial entry. In this study, observed median survival was 1.9-fold greater than expected in responding patients, and 3.4-fold longer in nonresponding patients.

IL-2 has been frequently given in conjunction with LAK cell adoptive immunotherapy. However, an analysis of 5 concurrent trials (Palmer et al. 1992a) indicated no therapeutic advantage was gained with LAK cell administration, and results from other studies support this conclusion (table IV). Palmer and colleagues (1992a) also observed a statistically significant increase in toxicity with the addition of LAK cell therapy. One randomised trial with a median follow-up period of 63 months, indicated there was no difference in the survival of patients with renal cell carcinoma who had received IL-2 with or without LAK cell therapy. In this study 24-month survival rates were 47% of patients receiving IL-2 plus LAK cells, and 40% of patients receiving IL-2 only, and 48-month survival rates were 29% and 25% of patients, respectively (Rosenberg et al. 1993). These results are higher than those reported in other studies with shorter follow-up periods; Dillman et al. (1993) reported a 40% 12-month survival in patients receiving IL-2 plus LAK cell therapy, and Palmer et al. (1992b) reported a 24-month survival of 24% and 28% in patients receiving IL-2 and IL-2 plus LAK cell therapy, respectively. It seems, therefore, that LAK cell therapy does not offer any clear therapeutic advantages, either in response rate or survival duration, compared to therapy with IL-2 alone.

The limited data evaluating IL-2 in combination with TIL therapy preclude definitive conclusions, but results to date indicate that significant advantages are unlikely. Objective response was 0 to 9% in patients given TIL and IL-2 in trials using low dosage regimens (Bukowski et al. 1991, 1993; Hanson et al. 1993b), whereas Dillman et al. (1993) concluded that TIL increased response rate but not survival. Kradin et al. (1989b) gave 7 patients with renal cell carcinoma intermediate dosages of IL-2 and TIL, and reported an objective response of 29%. Robertson and colleagues (1990) also administered intermediate dosages of IL-2 with or without TIL, and although the response rate was 25 to 30%, concluded there was no significant differences between groups.

Other combination therapies with IL-2 including IL-4 (Bukowski et al. 1993), IFN-γ (Escudier et al. 1993; Margolin et al. 1992), TNF (Dexeus et al. 1991; Rosenberg et al. 1989), cyclophosphamide (Lindemann et al. 1989; Rosenberg et al. 1989); vinblastine (Fink et al. 1992); anti-CD3 monoclonal antibody (Buter et al. 1993b; Hank et al. 1992), and polyinosinic-polycytidylic acid complexed with poly-L-lysine and carboxymethylcellulose (poly-ICLC) [Ewel et al. 1992] also do not appear to confer a therapeutic advantage in the preliminary studies to date. More recently, a combination therapy consisting of subcutaneous IL-2,

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Table V. Summary of trials in ≥20 patients[a] with advanced renal cell carcinoma receiving interleukin-2 (IL-2) in combination with interferon-alpha (IFN-α)

Reference	No. of evaluable patients	Dosage regimen ($\times 10^6$ IU/m^2/d)[b]	Period between cycles (weeks)	Response (% of patients)[c]				Objective response duration (months)
				objective	complete	partial	stable disease	
Atkins et al. (1993b)[d]	28	IL-2 14.4 $\times 10^6$ IU/m^2 + IFN-α 3 $\times 10^6$ IU/m^2 alt IVb q8h d1-5, 15-19		11	0	11		7-14
Atzpodien (1992)	>80	IL-2 20 SC d1-3 (ind) then 5 SC 3x per week q5w + IFN-α 3-6 SC 3x per week q5w		33	7	26	40	–[e]
Bukowski et al. (1993)	33	IL-2 0.1-26 IVb + IFN-α2a 0.1-10 IM 3x per week q4w		12	0	12		
Dutcher et al. (1993)	31	IL-2 5 $\times 10^6$ IU/m^2 SC q8h x 3, then daily 5x per week q4w + IFN-α 5 SC 3x per week q4w	2-4	16	3	13	32	>1.5->5
Enzinger et al. (1992)	30	IL-2 18 IVp alt. daily with IFN-α 10 SC d1-14	3-4	30	7	23		3->22
Faggiuolo et al. (1992)	20	IL-2 9-15 SC d1,2 (ind) then 4.5-4.8 SC d1-5 + IFN-α 3-6 SC 3x per week q6w	2	25	15	10	25	6->13
Figlin et al. (1992)	30	IL-2 2 IVc d1-4 q4w + IFN-α-2A 6 IM or SC d1,4 q4w	2	30	0	30	13	5.5->23
Ilson et al. (1992)	34	IL-2 6. IVc d1-4, q2w + IFN-α 5 SC d1-4, q3w (ind) then IL-2 12 IVc d1-5 + IFN-α 6 SC 3x per week q3w	2	12	3	9		>4->8
Kirchner et al. (1991a)	29	IL-2 14.4-18 SC d1,2, (ind) then 3.6-4.8 SC d1-5 q6w + IFN-α 3-5 SC 3x per week q6w		31	10	21	41	3->19
Lipton et al. (1993)	31	IL-2 1-4 IVc d1-5 + IFN-α 3-12 $\times 10^6$ IU/m^2 IM 2-3x per week q4w	2-4	42	19	23		5- >35

Table V. Contd

Reference	No. of evaluab patients
Négrier et al. (1991b)	35
Oldham et al. (1992) National Biotherapy Study Group	83
Pomer et al. (1991)	23
Pomer et al. (1992)	40
Raymond et al. (1993)	20
Rosenberg et al. (1989)	46
Sznol et al. (1992)	40

a Majority of patients h
b Unless otherwise stat
c Objective response =
response = disappear
d Results from one arm
e Median survival 19.6
f Patients also received
g Patients also received
h Patients also received
Abbreviations and symbo
IM = intramuscular inject
>15 min < 1 hour; mo =
n weeks; SC = subcutan

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leukin-2 (IL-2) in combination with

stable disease	Objective response duration (months)
	7-14
40	–[e]
32	>1.5->5
	3->22
25	6->13
13	5.5->23
	>4->8
41	3->19
	5- >35

Table V. Contd

Reference	No. of evaluable patients	Dosage regimen (x 10^6 IU/m^2/d)[b]	Period between cycles (weeks)	Response (% of patients)[c] objective	complete	partial	stable disease	Objective response duration (months)
Négrier et al. (1991b)	35	**IL-2 20 SC d1-3 (ind) then 5 SC 3x per week q5w** + IFN-α 3-6 SC 3x per week q5w		20	3	17		>2->8
Oldham et al. (1992) National Biotherapy Study Group	83	**IL-2 18 IVc d1-4.5** + IFN-α 3 SC d1,3,5	2	7	1	6		2.8 (median)
Pomer et al. (1991)	23	**IL-2 9 SC d1,2 (ind) then 4.5 SC** + IFN-α 3 SC d3,5,8,10,12,[f]		30	13	17	30	
Pomer et al. (1992)	40	**IL-2 18 SC d1-2** + IFN-α-2b 5 SC d1,3,5, (ind) then **IL-2 3.6 SC d1-5** + IFN-α-2b 5 SC d1,3,5 q6w[g]		28	13	15		
Raymond et al. (1993)	20	IFN-α-2b 10 x 10^6 IU IM d1-5 + **IL-2 18 IVc d6-10**		20	0	20	65	7-18 (median 11)
Rosenberg et al. (1989)	46	**IL-2 1-6 IU/m^2 q8h IVb d1-5, 14-18** + IFN-α 3-6 IVb d1-5, 14-18	8-12	33	9	24		
Sznol et al. (1992)	40	**IL-2 3-6 IVc d1-6, 12-17** + IFN-α-2a 12 SC 3x per week q3w[h]	1-4	20	0	20		2->26

a Majority of patients had undergone previous nephrectomy.
b Unless otherwise stated.
c Objective response = sum of complete and partial responses; complete response = disappearance of all measurable tumour; partial response = disappearance of ≥ 50% of all measurable tumour, stable disease = < 25% reduction or increase in all measurable tumour.
d Results from one arm of a randomised trial. Remainder of data shown in table IV.
e Median survival 19.6 mo.
f Patients also received ASI: 75 000 or NDV-cells ID 2x per week ≥ q2w.
g Patients also received modified autologous tumour material.
h Patients also received cyclophosphamide 300 mg/m^2, doxorubicin 25 mg/m^2 IVb d9 + LAK cells d 12,13,15.

Abbreviations and symbols: alt = alternating; ASI = active specific immunotherapy; d = day; ID = intradermal; IFN-α = interferon alpha; IM = intramuscular injection; ind = induction phase; IVb = intravenous bolus; IVc = continuous intravenous infusion; IVp = intravenous push >15 min < 1 hour; mo = month; MR = minor response, ≥ 25% reduction in measurable tumour; NDV = Newcastle disease virus; qnw = for n weeks; SC = subcutaneous injection.

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IFN-α and fluorouracil was administered in an outpatient setting, and 46% of 39 patients achieved an objective response. Preliminary results indicate a median response duration of >9 months, with no relapses observed in the 6 patients that achieved a complete response (Atzpodien et al. 1993). These promising results were obtained in a noncomparative, non-randomised study, and further studies are required to support these findings. In a series of 15 trials conducted by the National Biotherapy Study Group involving 788 patients with various cancers, IL-2 was administered by continuous infusion in conjunction with a series of other agents. In all 15 trials, IL-2 was administered at doses of 18×10^6 IU/m^2/day for cycles lasting 3 to 5 days, in protocols that included LAK and TIL adoptive immunotherapy, cyclophosphamide, IFN-α, TNF, or combination chemotherapy. 638 patients in total were evaluable for response, with responders receiving up to 6 cycles of treatment, and 13 of the 167 patients (8%) with renal cell carcinoma achieved objective response. In these patients, no particular protocol showed any survival advantage, and the overall median survival time was approximately 9 months (Dillman et al. 1993). Similarly, an evaluation of 10 trials involving 191 patients with renal cell carcinoma receiving IL-2 as monotherapy or in combination with IFN-α or IL-4, indicated an overall objective response rate of 12%. Survival or response duration were not reported in this evaluation, but no single protocol appeared to induce more favourable response rates (Bukowski et al. 1993).

Response rates in patients receiving IL2 plus IFN-α were comparable with IL-2 monotherapy (table V; Dillman et al. 1993; reviewed in Osterwalder 1992), as was response duration, which ranged between 3 and >35 months (Enzinger et al. 1992; Lipton et al. 1993), although median response durations of >19 months (Atzpodien & Kirchner 1991; Figlin et al. 1992) have been observed. Atzpodien et al. (1991c) reported that median survival was significantly longer (19.6 months) in patients receiving combination therapy with IFN-α than in patients receiving IL-2 alone (6.4 months); however, no objective responses were seen in the group receiving monotherapy. Further evidence does not support improved survival with IL-2 and IFN-α; in fact, a randomised comparative trial found that IL-2 monotherapy produced more durable responses (Atkins et al. 1993b). Noncomparative studies have also reported shorter response durations of 2 to 12 months with IL-2 and IFN-α alternating daily (Bergmann et al. 1991; Dazzi et al. 1991). There may, however, be a dose-dependent relationship with efficacy when IL-2 is used in combination with IFN-α. Enzinger and colleagues (1992) found a 30% objective response with an intermediate dosage regimen, compared with 8% with a low-dose regimen. Patients not achieving objective response had a median survival of 10 months (Figlin et al. 1992).

There is some uncertainty as to whether nephrectomy should precede or follow IL-2 therapy in patients with advanced renal cell carcinoma. Removal of the primary tumour prior to immunotherapy reduces tumour bulk, and thereby the number of cells to be eliminated, and may also remove a potential source of future metastases. Objective response rate was 15 to 20% in patients with nephrectomy prior to IL-2 therapy; however in one trial 37% of 54 patients were unable to receive immunotherapy due to complications related to the surgery or tumour (Robertson et al. 1990). In contrast, Spencer et al. (1992) found that immunotherapy was effective in the presence of primary tumours in a pilot study of 12 patients, but that no objective responses were possible in the primary tumour. Other investigators have concurred with these findings (Davis et al. 1990). Nonetheless, a patient achieving complete disappearance of metastases and >50% reduction in the primary tumour with high-dose IL-2 therapy prior to nephrectomy has been recently reported (Haas et al. 1993). In clinical trials to date, the majority of patients had undergone a prior nephrectomy. Although univariate analysis indicated prior nephrectomy was prognostic of survival in a group of 327 patients, multivariate analysis of the data did not identify nephrectomy as a significant prognostic factor (Palmer et al. 1992b).

Surgical resection of metastases has also been

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erapy produced more du-
:t al. 1993b). Noncompar-
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·wever, be a dose-depend-
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. Enzinger and colleagues
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ı median survival of 10
2).
ıinty as to whether neph-
ɔr follow IL-2 therapy in
'enal cell carcinoma. Re-
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ıinated, and may also re-
ɔf future metastases. Ob-
15 to 20% in patients with
! therapy; however in one
ere unable to receive im-
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'2) found that immuno-
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as a significant prognos-
ɔ92b).
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considered as an option after immunotherapy and subsequent relapse. In 16 patients with evidence of progressive disease following complete or partial response to immunotherapy, and who underwent surgical resection, the median time to disease progression was 11 months (Sherry et al. 1992). Of 11 patients who underwent resection of residual tumour after achieving partial responses to IL-2 therapy (and before relapse), all remained without evidence of disease for a median follow-up of 21 months. In contrast, 76% of 17 patients with complete responses and 35% of 34 patients with partial responses in the same trial who did not undergo surgery remained free of disease progression (Kim & Louie 1992). Candidates for surgery were selected individually and at varying periods (4 to 35 months) after the end of IL-2 therapy, and therefore the outcome may be somewhat biased. Not all patients are eligible for surgical resection, nevertheless, results in the small number of patients in this trial indicate a promising avenue for further research.

Comparative trials have usually studied efficacy differences between protocols containing IL-2, rather than between different agents. One study has compared survival in patients receiving IL-2 based therapy with patients receiving paclitaxel, and found that median 12-month survival with IL-2 was 50% compared with 33% of patients receiving paclitaxel (Walpole et al. 1993). However, this was not a randomised study, and therefore conclusions are limited. The comparative effect of dosage and different administration routes on clinical response are discussed further in section 4.

2.4 Malignant Melanoma

The incidence of malignant melanoma is increasing rapidly, with a 6-fold increase noted in the US during the past 50 years (reviewed in Rifkin et al. 1988). Although widespread public and health care education programmes are improving early detection and treatment, the prognosis remains poor for patients who have progressed to metastatic disease. Surgical excision can be curative for localised tumours, but chemotherapy and immunotherapy, or combination therapy appear to be the best treatment options for metastatic melanoma.

IL-2 monotherapy has been studied in a number of trials in patients with metastatic melanoma, and those with ≥20 evaluable patients are listed in table VI. As for renal cell carcinoma, the combination of IL-2 and adoptive immunotherapy offered no clear therapeutic advantage, nor was clinical response conclusively dose-dependent. Objective response rate was approximately 13% overall (range 3 to 24%), with a variable response duration. Less than 3% of patients achieved complete responses, but response duration was considerably longer in these patients, with a number remaining clinically free of disease for >2 years. Nonresponding patients usually died within 6 to 8 months. Intrasplenic infusion, bolus injection or continuous intravenous infusion have been used to deliver IL-2 in melanoma patients but, at present, therapeutic advantages with these methods of administration are not evident. Normothermic isolation perfusion achieved a 70% objective response rate (1 complete response, 6 partial responses) in 10 patients with relapsed or refractory melanoma, and all patients were alive after a follow-up period of 4 to 27 months (Arienti et al. 1993). Further studies are required to confirm the auspicious but preliminary findings with this method of IL-2 administration.

IL-2 has been given to patients with metastatic melanoma in conjunction with a wide variety of agents (table VII). As for IL-2 monotherapy, complete responses in patients receiving combination therapy appear to be more durable than partial responses, which tended to relapse after approximately 6 months in most trials (Demchak et al. 1991; Dillman et al. 1991a; Flaherty 1989). However, with combination therapy the schedule of administration may be important; Keilholz and colleagues (1992a) found that toxicity was reduced and response rate was enhanced when IL-2 was given in large initial doses with a rapid decrease in dose over 2 days, compared with the same total dose given at a steady rate over the 5-day period. Nevertheless, synergy was rarely seen between cytokines in human studies, and high- and low-dose combinations of IL-2 and IFN-α appear to be no

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Table VI. Summary of trials in ≥20 patients[a] with metastatic malignant melanoma receiving interleukin-2 (IL-2) with or without adoptive immunotherapy

Reference	No. of evaluable patients	Interleukin-2 (x 10^6 IU/m²/d)[b]	Period between cycles (weeks)	Adoptive immunotherapy	Response (% of patients)[c] objective	complete	partial	Objective response duration (months)	Comment
Bar et al. (1990)	50	6 x 10^5 IU/kg IVb q8h d1-3, then 18 IVc d9-15	12	LAK	14	2	12	>1->24	
Dillman et al. (1991b)	33	18 IVc d1-5, 11-15	2	LAK	12	6	6	7->27	Overall median survival 6.1mo
Dorval et al. (1992)	27	18-20 IVc d1-5, 15-20	3		22	7	15	4->42	10/27 had DTIC 800 mg/m² 3d before IL-2
Dutcher et al. (1989)	32	6 x 10^5 IU/kg IVb q8h d1-5, 12-16	12	LAK	19	3	16	1->31	6% MR, 12% SD
Dutcher et al. (1991)	33	18 IVc d1-4.5, then 22.5 IVc d11-15	12	LAK	3	0	3	10	
Gaynor et al. (1990) NC-L287-69 (Multicenter USA)	30	18 IVc d 1-4.5 (ind) then 18-27 IVc d11-16	10	LAK	3	0	3	8	
Parkinson et al. (1990a)	46	6 x 10^5 IU/kg IVb q8h d1-5, 12-16	12		22	4	19	4->20	
Rosenberg et al. (1989)	42	6 x 10^5 IU/kg IVb q8h d1-5, 14-18	8-12		24	0	24	2->41	
	48	6 x 10^5 IU/kg IVb q8h d1-5, 14-18	8-12	LAK	21	8	13	2->52	
Sparano et al. (1993b)[d]	44	6 x 10^6 IU/m² IVb q8h d1-5, 15-19			5	0	5	2->15 (median 11.5)	Overall median survival 10.2mo
Thatcher et al. (1989)	31	6-96 intrasplenic then IVp d1,3,5,7	2		3	0	3		35% SD
Whitehead et al. (1991)	42	36-60 1Vb d1,3,5	0		10	0	10		21% SD median survival 9.9mo

a Majority of patients had undergone previous tumour excision.
b Unless otherwise stated.
c Objective response = sum of complete and partial responses; complete response = disappearance of all measurable tumour; partial response = disappearance of ≥ 50% of all measurable tumour
d Results from 1 arm of a randomised trial. Remainder of data shown in table VII.
Abbreviations and symbols: CYC = cyclophosphamide; d = day; DTIC = dacarbazine; Ind = induction phase; IVb = intravenous bolus ≤ 15 mins; IVc = continuous intravenous infusion; IVp = intravenous push >15 min < 1 hour; LAK = activated peripheral blood mononuclear cells; mo = months; MR = minor response, ≥ 25% reduction in measurable tumour; q8h = every 8 hours, SC = subcutaneous injection; SD = stable disease; TIL = tumour infiltrating lymphocytes.

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a Majority of patients had undergone previous tumour excision.
b Unless otherwise stated.
c Objective response = sum of complete and partial responses; complete response = disappearance of all measurable tumour; partial response = disappearance of ≥ 50% of all measurable tumour
d Results from 1 arm of a randomised trial. Remainder of data shown in table VII.
Abbreviations and symbols: CYC = cyclophosphamide; d = day; DTIC = dacarbazine; ind = induction phase; IVb = intravenous bolus ≤ 15 mins; IVc = continuous intravenous infusion; IVp = intravenous push >15 min < 1 hour; LAK = activated peripheral blood mononuclear cells; mo = months; MR = minor response, ≥ 25% reduction in measurable tumour; q8h = every 8 hours; SC = subcutaneous injection; SD = stable disease; TIL = tumour infiltrating lymphocytes.

more effective than either agent as conventional monotherapy (Sparano et al. 1993b; Whitehead et al. 1993). Subcutaneous administration of low-dose IL-2 and IFN-α has resulted in objective response rates from 0% (Castello et al. 1993) to 33% (Ron et al. 1992).

In 15 trials using IL-2 in various combination regimens reported by Dillman et al. (1993), 33 of 188 evaluable patients (18%) with melanoma achieved objective responses, but no single protocol showed clear survival advantage. Combination therapies included LAK and TIL adoptive immunotherapy, cyclophosphamide, IFN-α, TNF, or combination chemotherapy, and the overall median survival time was approximately 9 months with 35% of patients surviving 1 year. A combination of IL-2, cisplatin, and IFN-α may be more effective: 54% of 39 patients achieved objective responses (including 13% complete responses) with a median survival of approximately 11 months (Antoine et al. 1993). A preliminary report of the use of IL-2 and TIL after a single intravenous dose of cyclophosphamide, achieved a very promising 60% objective response rate in 15 patients with malignant melanoma, who had not received IL-2 previously. In the same trial, 2 of 5 patients who had failed to respond to previous IL-2 therapy, also achieved partial responses with this new protocol; however, the effect on survival has yet to be determined (Rosenberg et al. 1988). A more recent preliminary study reported a response rate of 21% in 19 patients using a similar regimen; survival data were not available (Hanson et al. 1993a). Small trials have been performed with other agents in combination with IL-2; flavone acetic acid (O'Reilly & Rustin 1991), indomethacin (Mertens et al. 1992), carboplatin, cisplatin and IFN-α (Kirchner et al. 1991c), but no marked improvement in patient survival has been noted.

Notwithstanding, chemoimmunotherapy has yielded some promising results, and most of these have been observed in trials using IL-2 in combination with several agents. Richards et al. (1992) reported an objective response rate of 59% with combination therapy using carmustine, dacarbazine, cisplatin, IFN-α and IL-2. Despite these results, the overall median survival for the 34 evaluable patients was only 10.3 months. Hamblin and colleagues (1991) also published a preliminary report of 12 patients who achieved an objective response rate of 86% with dacarbazine, cisplatin, IFN-α, and IL-2 in intermediate dosage regimens. Two of 3 patients who achieved complete responses in this study relapsed early after treatment with cerebral metastases, but the other patient with a complete response remained in remission for >14 months. It is evident from the larger trials listed in table VII, that although the average response rate with chemoimmunotherapy is approximately 36%, investigators have used various combinations of agents, making it difficult to determine the comparative efficacy of any one regimen.

In summary, it is evident that the ideal dosage regimen and combination of agents has not been identified; however, there are several promising possibilities. In general, the response rate of patients with malignant melanoma to IL-2 therapy indicates that it is a useful adjunct to other available therapeutic options for these patients.

2.5 Colorectal Cancer

Colorectal carcinoma is the second most common malignancy in the US, accounting for approximately 15% of all cancers. Survival appears to depend on the extent of the disease at diagnosis, with the 50% of patients who present with advanced disease having a median overall survival of 6 to 10 months (reviewed in Wadler 1991). Treatment of patients with advanced colorectal cancer is largely unsuccessful, with most therapies having little impact on patient survival. Fluorouracil has been the most widely used agent in patients with this disease, and IL-2 has frequently been given in conjunction with this agent.

In 15 trials in patients with a variety of cancer types, the National Biotherapy Study Group reported that only 1 of 76 patients with colorectal cancer achieved an objective response after receiving IL-2 and IFN-α (Dillman et al. 1993). Trials in a total of 54 evaluable patients with colorectal cancer who received IL-2 and IFN-α subcutaneously

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Table VII. Summary of trials in ≥20 patients with metastatic malignant melanoma receiving interleukin-2 (IL-2) in combination with other agents

Reference	No. of evaluable patients	Dosage regimen	Period between cycles (weeks)	Response (% of patients)[a] objective	complete	partial	Objective response duration (months)	Comment
Antoine et al. (1993)[b]	39	CDDP 100 mg/m^2 IV d1 + IL-2 18 x 10^6 IU/m^2/d IVc d3-6, 7-21 + IFN-α 9 x 10^6 IU SC 3x per week	5	54	13	41	5->8	Median survival 11mo
Atkins et al. (1993a)	38	CDDP 50 mg/m^2, DTIC 350 mg/m^2 IV d1-3, 43-45 + IL-2 6 x 10^5 IU/kg IVb q8h d12-16, 26-30 + tamoxifen 20 mg/d PO	3-4	42	8	34	2->10	
Bajorin et al. (1990)	20	IL-2 6 x 10^6 IU/m^2/d IVp d1-5, 8-12 + R24 1-12 mg/m^2 IV d8-12		5	0	5	6	10% MR
Bukowski et al. (1993)	23	IL-2 0.1-26 x 10^6 IU/m^2 IVb + IFN-α2a 0.1-10 IU/m^2 IM 3x per week q4w		26	9	17		
Demchak et al. (1991)	27	IL-2 6 x 10^5 IU/kg IVb q8h d1-5, 15-19 + CDDP 135-150 mg/m^2 IVp + WR-2721 910 mg/m^2 IV d32,53 or IL-2 6 x 10^5 IU/kg IVb q8h d1-5, 15-19 + CDDP 50 mg/m^2 IV 2hrs, d32-34, 53-55		37	11	26	1->30	
Dillman et al. (1990) NBSG 87-11 trial	27	IL-2 18 x 10^6 IU/m^2/d IVc d1-5, 11-15 + d1-5 q6w + LAK d11-13; + DTIC 1200 mg/m^2 total IVp d27, or d27,28, or d27-29	3	26	7	19	3->24	11% SD, median survival 10mo
Dillman et al. (1991a)	21	CYC 1g/m^2 d1 + IL-2 18 x 10^6 IU/m^2/d IVc d1-4 + TIL d2	3	24	5	19	2-7	5% MR, 29% SD
Flaherty et al. (1990)	32	DTIC 1 g/m^2/d IVc d1, + IL-2 12-30 x 10^6 IU/m^2/d IVp d15-19, d22-26	0	22	3	19	2->22 (median 4.7)	Overall median survival 8.5mo

Table VII. Contd

Reference	No. of evaluable patients	Dosage regimen	Period between cycles (weeks)	Response (% of patients)[a] objective	complete	partial	Objective response duration (months)	Comment
Flaherty et al. (1993)		DTIC 750 mg/m^2, CDDP 100 mg/m^2 IVb d1 + IL-2 24 x 10^6	1-6	41	16	25	3->20 (median 8)	Overall median survival 10.2mo

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Reference	No. of evaluable patients	Dosage regimen	Period between cycles (weeks)	objective	complete	partial	Objective response duration (months)	Comment
		d27-29						
Dillman et al. (1991a)	21	CYC 1g/m^2 d1 + **IL-2 18 x 10^6 IU/m^2/d IVc d1-4** + TIL d2	3	24	5	19	2-7	5% MR, 29% SD
Flaherty et al. (1990)	32	DTIC 1 g/m^2/d IVc d1, + IL-2 **12-30 x 10^6 IU/m^2/d IVp d15-19, d22-26**	0	22	3	19	2->22 (median 4.7)	Overall median survival 8.5mo

Table VII. Contd

Reference	No. of evaluable patients	Dosage regimen	Period between cycles (weeks)	Response (% of patients)[a]			Objective response duration (months)	Comment
				objective	complete	partial		
Flaherty et al. (1993)		DTIC 750 mg/m^2, CDDP 100 mg/m^2 IVb d1 + **IL-2 24 x 10^6 IU/m^2/d IVp d12-16, 19-23**	1-6	41	16	25	3->20 (median 8)	Overall median survival 10.2mo
Keilholz et al. (1992a)	a) 27 b) 27	a) IFN-α 10 x 10^6 IU/m^2/d SC d1-5 + **IL-2 18 x 10^6 IU/m^2/d IVc d6-11** b) IFN-α 10 x 10^6 IU/m^2/d SC d1-5 + **IL-2 4.5-72 x 10^6 IU/m^2/d, IVc dec. d6-11**	4	a) 18 b) 41	a) 4 b) 11	a) 15 b) 30		a) 15% SD, median survival 11mo b) 19% SD, median survival >14mo
Kirchner et al. (1993)	40	Carboplatin 400 mg/m^2, DTIC 750 mg/m^2 IV d1, 22 + **IL-2 5-20 x 10^6 IU/m^2 SC 3x per week** + IFN-α 6 x 10^6 IU/m^2 SC 3x per week q6w		35	8	27	3->27	40% SD
Kruit et al. (1991)	54	**IL-2 3 x 10^6 IU/m^2/d IVc d1-4** IFN-α 6 x 10^6 IU/m^2/d d1,4	1	20	2	18		35% SD
Mitchell et al. (1988)	24	CYC 350 mg/m^2 IVb d1 + **IL-2 21.6-73.2 (Inc) x 10^6 IU/m^2/d IVb d4-8, 12-16**	1	25	4	20	1->12 (median >5)	33% MR
Richards et al. (1992)	34	Carmustine 150 mg/m^2 IV d1 + DTIC 220 mg/m^2, CDDP 25 mg/m^2 IV 2hrs d1-3, 22-24 + **IL-2 1.5 x 10^6 IU/m^2 q8h IVb** + IFN-α 6 x 10^6 IU/m^2 SC d4-8, 17-21 + tamoxifen 10mg PO bd q6w		59	24	35	5->10 (median >7->9)	Overall median survival 10.3mo
Rosenberg et al. (1988)	20	CYC 25mg/kg IVb d1, TIL IVb d4-6, + **IL-2 6 x 10^5 IU/kg q8h IVb d5-10**		55	5	50	2->13	2/5 patients responded after previous IL-2 therapy

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Table VII. Contd

Reference	No. of evaluable patients	Dosage regimen	Period between cycles (weeks)	Response (% of patients)[a] objective	complete	partial	Objective response duration (months)	Comment
Rosenberg et al. (1989)	44	**IL-2 1-6 x 10^6 IU/m^2 q8h IVb d1-5, 14-18** + IFN-α 3-6 x 10^6 IU/m^2/d IVb d1-5, 14-18	8-12	36	7	30		
Sparano et al. (1993b)[c]	41	**IL-2 4.5 x 10^6 IU/m^2 q8h IVb d1-5, 15-19** + IFN-α 3 x 10^6 IU/m^2 q8h IVb d1-5, 15-19		10	0	10	2->15 (median 11.5)	Overall median survival 9.7mo
Stoter et al. (1989)	24	**IL-2 18 x 10^6 IU/m^2/d IVc d1-5, 12-17** + DTIC 850 mg/m^2 IVb d26	5	25	8	17	2-13	21% SD, Overall median survival 13mo
Sznol et al. (1992)	40	**IL-2 3-6 x 10^6 IU/m^2/d IVc d1-5, 12-17** + CYC 300 mg/m^2, doxorubicin 25 mg/m^2 IVb d9 + LAK d12,13,15, + IFN-α-2a 12 x 10^6 IU/m^2 SC 3x per week q3w	1-4	20	0	20	2->26	
Verdi et al. (1992)	23	CYC 350 mg/m^2 IVb d1, + **IL-2 18-36 x 10^6 IU/m^2 (inc) IVb d4-8, 11-15**	1	4	0	4	<4	

a Objective response = sum of complete and partial responses; complete response = disappearance of all measurable tumour; partial response = disappearance of ≥50% of all measurable tumour.
b A further 19 patients were given the same regimen plus tamoxifen with no added improvement in response rate.
c Results from 1 arm of a randomised trial. Remainder of data shown in table VI.
Abbreviations and symbols: bd = twice a day; CDDP = cisplatin; CYC = cyclophosphamide; d = day; dec = decreasing doses; DTIC = dacarbazine; hrs = over n hours; IFNα = interferon-alpha; inc = in increasing doses; IVb = intravenous bolus ≤15 min; IVc = continuous intravenous infusion; IVp = intravenous push >15 min <1 hour; LAK = activated peripheral blood mononuclear cells; MR = minor response, ≥25% reduction in measurable tumour; NBSG = National Biotherapy Study Group; PO = orally; qnw = for n weeks; R24 = mouse monoclonal antibody against ganglioside G_{D3}; SC = subcutaneous injection; SD = stable disease; TIL = tumour infiltrating lymphocytes; WR-2721 = S2(3-aminopropyl-amino) ethylphosphorothioic acid.

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a Objective response = sum of complete and partial responses; complete response = disappearance of all measurable tumour; partial response = disappearance of ≥50% of all measurable tumour.

b A further 19 patients were given the same regimen plus tamoxifen with no added improvement in response rate.

c Results from 1 arm of a randomised trial. Remainder of data shown in table VI.

Abbreviations and symbols: bd = twice a day; CDDP = cisplatin; CYC = cyclophosphamide; d = day; dec = decreasing doses; DTIC = dacarbazine; hrs = over n hours; IFNα = interferon-alpha; inc = in increasing doses; IVb = intravenous bolus ≤15 min; IVc = continuous intravenous infusion; IVp = intravenous push >15 min <1 hour; LAK = activated peripheral blood mononuclear cells; MR = minor response, ≥25% reduction in measurable tumour; NBSG = National Biotherapy Study Group; PO = orally; qnw = for n weeks; R24 = mouse monoclonal antibody against ganglioside G_{D3}; SC = subcutaneous injection; SD = stable disease; TIL = tumour infiltrating lymphocytes; WR-2721 = S2(3-aminopropyl-amino) ethylphosphorothioic acid.

followed by fluorouracil infusion, achieved objective response rates of 10% (Navone et al. 1993) and 15% (Goey et al. 1993). Objective response was not achieved in 36 patients with colorectal cancer taking part in 10 trials with IL-2 in combination with IFN-α, TIL, IL-4, or doxorubicin (Bukowski et al. 1993), nor in 13 patients who received IL-2 plus melatonin (Barni et al. 1992). Other trials have, however, reported higher rates of success. Of 42 patients who received either IL-2 monotherapy, or IL-2 plus LAK therapy, 5 objective responses were seen, all within the group that received the combination therapy (Rosenberg et al. 1989). Objective responses with combination IL-2 and LAK therapy have been noted in other trials with Margolin and colleagues (1989) reporting a 12% response in 22 patients, and Steis et al. (1990) observing a 42% response in 12 patients. Partial response was also achieved by 1 of 10 patients that received IL-2 in combination with IFN-α (Rosenberg et al. 1989). No responses were seen in the 6 patients who received TNF and IL-2 concomitantly (Rosenberg et al. 1989), nor were responses noted in 9 patients receiving IFN-γ and IL-2 (Hu et al. 1990).

A combination of IL-2, fluorouracil, and calcium folinate may be more effective than chemotherapy or immunotherapy alone. 11 of 23 patients (44%) achieved objective responses with this protocol, and 2 were complete responses of 15 and 24 months' duration. Partial response durations averaged 10 months for the patients in this study (Yang et al. 1993). In another study, 2 of 7 patients with colorectal cancer who received infusions of IL-2 18 × 10^6 IU/m^2/day for 5 days followed by 3 (weekly) boluses of fluorouracil 600 mg/m^2, achieved partial responses, and 3 patients had stable disease (Hamblin et al. 1989). An objective response rate of 13% was attained in 23 patients who received a protocol of IL-2, fluorouracil and calcium folinate, and a further 5 patients achieved minor responses or stable disease (Hiddemann et al. 1991). However, a randomised comparative trial comparing fluorouracil plus calcium folinate with or without IL-2, achieved response rates of 16% (2 complete responses, 8 partial responses) in patients receiving IL-2, and 12% (4 complete responses, 4 partial responses) in patients receiving only fluorouracil and calcium folinate. 127 patients in total were evaluable, and response duration was 8 and 7 months, respectively, with median survival 14 and 12 months (Eremin et al. 1993). Other investigators have used a combination of IL-2, fluorouracil, calcium folinate and thymopentin with promising initial results: 4 of 8 evaluable patients achieved partial responses, and 2 patients had stable disease (Lopez et al. 1991).

In summary, the most useful results in advanced colorectal cancer so far appear to be with a combination of IL-2 and LAK cell therapy, or with immunotherapy combined with chemotherapy. However, there is little information available about the comparative survival rates with these different protocols, and the more recent data in larger numbers of patients is less encouraging. To date, no major trials have reported the use of TIL in patients with colorectal carcinoma, and research suggests that although TIL from colon cancer respond well to IL-2 expansion, they are only weakly cytotoxic against fresh colon carcinoma cells (Yoo et al. 1990). The use of IL-2 perioperatively has been suggested, as these patients are usually immunocompromised before surgery, and, in addition, surgery may promote tumour growth (Brivio et al. 1992; Eggermont et al. 1987a; Guillou 1988). Initial studies in small numbers of patients indicated that IL-2 18 × 10^6 IU/m^2/day perioperatively was well tolerated, and effectively prevented immunosuppression (Brivio et al. 1992, 1993). Further studies are required to confirm these preliminary findings.

2.6 Ovarian Cancer

Therapeutic strategies for patients with ovarian cancer have included radiotherapy, surgery, and a variety of systemic agents. Current therapy for ovarian cancer often involves more than one approach; for example, cytoreductive surgery (surgical debulking) followed by combination chemotherapy. A good response to chemotherapy can be achieved in approximately 80% of patients; notwithstanding, >80% of patients who present with

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advanced ovarian cancer survive less than 5 years (de Dycker et al. 1991). Immunotherapeutic studies performed with IL-2 are aimed at improving survival and reducing the development of peritoneal ascites, a common occurrence in advanced ovarian cancer.

To date, experience with intravenous IL-2 in patients with ovarian cancer is limited. Panici et al. (1989) reported one complete response in four evaluable patients with ovarian cancer, who received continuous infusions of IL-2 18×10^6 IU/m^2/day with 6-day rest periods between cycles. A total of 11 patients enrolled in this trial; however, five patients discontinued therapy due to disease progression or unacceptable toxicity. All patients received IL-2 after pretreatment with surgery and chemotherapy, and had minimal residual disease (tumour <2cm) at second-look surgery.

A phase II study in 10 patients with unresectable ovarian cancer evaluated the toxicity and efficacy of cisplatin 100 mg/m^2 and cyclophosphamide 600 mg/m^2, followed by a 5-day intravenous infusion of IL-2 18×10^6 IU/m^2/day, with a 2-week rest period before and after the IL-2 infusion. All patients in the trial experienced severe adverse events which significantly influenced their compliance with therapy and required intensive monitoring. No efficacy data are available to date (de Dycker et al. 1991). In other trials, no objective responses were seen in a total of 4 patients with ovarian cancer (Lotze et al. 1986; Oldham et al. 1991; Rosenberg et al. 1989). One of 15 patients with ovarian cancer in a series of 15 trials achieved partial response; the response duration was only one month (Dillman et al. 1993).

Intraperitoneal administration of antineoplastic agents is considered useful in treating ovarian tumours, as this cancer is typically confined to the abdominal cavity. The intraperitoneal route is thought to increase the ratio of peritoneal to systemic exposure to the drug, and may thereby limit the systemic toxicity that is common with IL-2. High levels of soluble IL-2 receptor have been detected in the ascitic fluid of these patients, which may in part explain the poor antitumour effects of infiltrating lymphocytes (Barton et al. 1993). Patients with advanced ovarian cancer often develop malignant peritoneal effusions, and one of the goals in the palliative management of these patients is to increase the time between effusion drainage. Intraserous IL-2, given after drainage of the effusion has been shown to be effective in prolonging the time between drainages (Barni et al. 1991).

Unfortunately, results of small trials with IL-2 have not indicated major improvements in patient survival. 10 patients with unresectable ovarian cancer were enrolled in a phase I trial of intraperitoneal IL-2 and LAK cell therapy. After treatment, 9 of these patients had progressive disease, and the single patient who demonstrated tumour reduction developed progressive disease after 3 months. Overall survival was 2 to >27 (median >11) months (Stewart et al. 1990). Prior intravenous infusions of IL-2 may, however, increase the response rate. Two of 10 patients with ovarian cancer achieved partial responses (determined by laparoscopy).

A pilot clinical protocol was initiated in 1991 in patients with epithelial ovarian cancer who failed to respond to at least one regimen of chemotherapy. The protocol compared IL-2 with IL-2 plus TIL administered intraperitoneally, and a preliminary report indicated a cytopathological response in four patients treated with IL-2 and TIL. Effects on survival have not yet been published (Freedman 1991, Freedman et al. 1992, 1993). Some investigators have raised concerns that intraperitoneal administration of IL-2 may increase the development of peritoneal fibrosis, leading to adhesions (Urba et al. 1989), perhaps by the IL-2-induced production of fibrogenic cytokines (Kovacs et al. 1993); others suggest adhesions are more likely to be due to the natural progression of the disease (Stewart et al. 1990).

In conclusion, data are at present insufficient to determine the role of IL-2 in the treatment of ovarian cancer.

2.7 Bladder Cancer

Bladder cancer is the fourth most common cancer in humans, and 49 000 new cases in the US in 1990 were estimated (Cockett et al. 1991). In early

studies, IL-2 was ad
later trials intravesic
tration were more co
involves surgery and
(BCG) therapy, whic
development of acti
cally.

Intralesional injec
in reducing the size o
few adverse reaction
al. 1984). In 3 of 6
were seen, lasting for
patients achieved a 7
(Pizza et al. 1984). A
for advanced transit
travesical continuou
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studies, IL-2 was administered intralesionally; in later trials intravesical and intra-arterial administration were more common. Current therapy often involves surgery and/or bacillus Calmette-Guerin (BCG) therapy, which is thought to stimulate the development of activated lymphocytes intravesically.

Intralesional injection of IL-2 proved effective in reducing the size of small, localised tumours with few adverse reactions (Fujioka et al. 1988; Pizza et al. 1984). In 3 of 6 patients, complete responses were seen, lasting for >2 to >7 months, and 2 other patients achieved a 70% regression of tumour mass (Pizza et al. 1984). An alternative approach used for advanced transitional cell carcinoma was intravesical continuous infusions of IL-2 following transurethral resection of the tumour. Using this protocol with high dosages of natural IL-2, Huland and Huland (1989) reported a complete response lasting >6 months in 1 of 5 patients, with no adverse effects. Intravesical IL-2 885 U/day plus BCG 60 mg/day for 6 weeks achieved complete response rates of 80 and 88% in patients with carcinoma *in situ* (5 patients) or recurrent superficial cancer (17 patients), respectively, whereas only 59% of 22 patients receiving BCG monotherapy achieved complete responses, as determined by cystoscopy and biopsy (Cockett et al. 1991). Patients received maintenance therapy every month for 1 year, with a reduced treatment frequency in subsequent years; however, as patients with positive biopsies or cytology received additional BCG treatment, it was uncertain whether the difference in the response rates could be solely attributed to IL-2. Another study of 9 patients with metastatic bladder cancer receiving IL-2 18×10^6 IU/m^2/day by continuous intravenous infusion over two 5-day periods combined with LAK cell therapy, reported no objective responses (Hermann et al. 1992). However, in this study the cancer was advanced (all patients died within 2 to 14 months; median 10 months), and substantial changes were seen in lymphocyte subsets in the blood and within tumours after treatment, despite the lack of clinical response.

It has been suggested that treatment may be more efficient in localised, low-stage bladder cancer, and this viewpoint was reinforced by a study in 12 patients with low-stage transitional cell carcinoma who received intra-arterial IL-2 before transurethral resection. Dosages up to 18×10^6 IU/m^2/day were given via the internal iliac artery as 5-day continuous infusions, and 2 complete responses and 3 partial responses were obtained, with all other patients achieving stable disease. During a mean follow-up of 23 months, 2 patients had a local recurrence 3 months after the transurethral resection (Tubaro et al. 1991; Velotti et al. 1991). However, a recent multicentre study in patients with superficial transitional cell carcinoma of the bladder was less successful. Intravesical instillation of IL-2 after transurethral resection achieved complete response in 4 of 35 patients, and 15 patients showed progressive disease (Boccon-Gibod et al. 1993).

Patients with bladder cancer who have been included in trials in patients with a variety of neoplastic disease have not shown objective responses, but numbers are too small for conclusions to be made (Oldham et al. 1991; Paciucci et al. 1989; Tamura et al. 1989; Taylor et al. 1992). At present therefore, the efficacy of IL-2 in the treatment of bladder cancer is not established, but initial results in patients with early or low-stage pathology, and with intravesical administration, require further exploration.

2.8 Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas are a diverse group of neoplasms that originate primarily from B cells, with differing rates of progression and response to therapy (reviewed in Armitage 1993). IL-2 therapy in patients with these disorders looked promising in early trials, with 1 complete response and 5 partial responses in 10 evaluable patients (Allison et al. 1989; Rosenberg et al. 1987; West et al. 1987). However, more recent reports have not been so optimistic (Bernstein et al. 1991; Duggan et al. 1992; Lim et al. 1991c; Margolin et al. 1991). The majority of these studies administered medium or high dose IL-2 by intravenous bolus or continuous infusion.

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IL-2 plus LAK cell therapy in patients with refractory, progressive non-Hodgkin's lymphoma (n = 12) produced a partial response in 1 patient with diffuse large cell non-Hodgkin's lymphoma, with 4 patients achieving stable disease (Bernstein et al. 1991). Similarly, Margolin et al. (1991) reported no responses in 15 patients with non-Hodgkin's lymphoma but 2 partial responses in 12 patients with Hodgkin's disease, receiving IL-2 plus LAK cell therapy. In contrast, other studies have found that no patients with Hodgkin's disease or diffuse large cell non-Hodgkin's lymphoma responded, but that patients with follicular disease achieved objective responses (Tourani et al. 1991; Weber et al. 1992). Levy et al. (1992), however, reported 5 objective responses (1 complete response, 4 partial responses) in 10 patients with low-grade follicular disease receiving IL-2 monotherapy, although all 7 patients with diffuse large-cell lymphoma had progressive disease.

A preliminary report comparing the response of IL-2 with or without LAK cell therapy in patients with low-grade or aggressive disease, observed 1 complete response in 17 patients with low-grade non-Hodgkin's lymphoma, whereas 3 complete responses and 2 partial responses were seen in 19 patients with aggressive disease. In addition, 2 of 4 patients with mycosis fungoides achieved complete responses (Gisselbrecht et al. 1992). The effect of concomitant LAK cell therapy in this trial was not discussed. However, in 19 patients treated with either intravenous IL-2 7.2×10^5 IU/kg every 8 hours (n = 11) or the same dosage of IL-2 plus LAK cell therapy (n = 8), no patients responded to monotherapy, but the IL-2 and LAK group achieved 1 complete response and 3 partial responses. Subsequent relapse in 3 responders was effectively treated with the same regimen, and all responders were alive at >30 to >62 months of follow-up (Weber et al. 1992).

Other combination therapy regimens have been used in a few preliminary studies. IL-2 therapy with or without IFN-β has been administered with limited success to 41 patients with non-Hodgkin's lymphoma in a randomised trial. Severe, life-threatening toxicity was experienced by 17 patients, and there were 3 treatment-related deaths. Four objective responses (1 complete response, 3 partial responses) were achieved in patients receiving IL-2 only, and 3 patients in the combination therapy group responded (1 complete response, 2 partial responses) yielding an overall response rate of 17%. Overall median survival was 4.3 and 9.3 months, respectively, with responses lasting between 83 and 402 days (Duggan et al. 1992). Patients have also been given IL-2 in combination with anti-CD19 antibody with 1 partial response and 4 minor responses observed in 6 patients with low-grade non-Hodgkin's lymphoma (Rankin et al. 1991).

At present therefore, small patient numbers and conflicting results in studies preclude any conclusions about the role of IL-2 in the treatment of non-Hodgkin's lymphoma.

2.9 Acute Myeloid Leukaemia

In vitro studies have indicated that IL-2 therapy may have the potential to eradicate leukaemic blast cells, and may therefore be useful in the treatment of acute myeloid leukaemia (AML) [Atzpodien et al. 1991a; Findley et al. 1988; Foa et al. 1992b; Lotzová et al. 1991]. However, the potential benefits of IL-2 therapy could be ineffective if the cytokine at the same time acted as a growth factor for the malignant cells. This is a possibility in acute lymphoid leukaemia and lymphoma (Tiberghien et al. 1992), but is thought to be less likely in AML, as studies have shown that cells from patients with AML tend to express either the low-affinity p55 or intermediate-affinity p75 receptor chains, but not both simultaneously (reviewed in Brenner 1991). IL-2 therapy has been used as induction therapy to achieve remission, and as consolidation or maintenance therapy after the achievement of remission with other agents.

A pilot study indicated that IL-2 therapy was effective in inducing clinical responses in patients with limited disease, but was less useful in patients with advanced disease with resistant blast cells. 12 patients with AML received IL-2 in escalating doses by continuous 5-day infusions. Three of 5 patients with limited disease (8 to 15% marrow blast cells)

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Data concerning the role of IL-2 in maintenance and consolidation therapy are also available in small groups of patients, and other research is in progress (Ganser et al. 1993). Three patients who were treated with IL-2 while in their first complete responses after chemotherapy remained in complete remission, whereas 2 of 4 patients treated during their second complete responses relapsed within 4 months of IL-2 therapy (Lim et al. 1992). In contrast, 4 of 12 patients receiving IL-2 as consolidation therapy maintained a longer second than first remission, with a mean response duration of 16 months (Bergmann et al. 1993). Preliminary results indicate that IL-2 therapy after autologous bone marrow transplantation may reduce the risk of relapse in patients with AML. After an 18-month period following bone marrow transplantation 7 patients who received IL-2 had a 71% disease-free survival rate, compared with a 36% disease-free survival rate in 11 patients who did not receive IL-2 (Hamon et al. 1993). Two of 3 children with AML receiving IL-2 after autologous bone marrow transplantation relapsed within 11 months, but the remaining patient continued in remission for more than 23 months of follow-up. In this study, the duration of the second complete response after IL-2 therapy exceeded the first complete response duration in 2 of 3 patients (Meloni et al. 1992).

In summary, data available in small groups of patients indicate that there may be a role for IL-2 in the treatment of AML, particularly in prolonging response duration, but further clarification is required.

3. Tolerability

The significant adverse events associated with systemic IL-2 therapy demand intensive monitoring, and limit treatment to those patients sufficiently robust to tolerate a wide range of adverse effects. Notwithstanding, much effort has been expended in managing, limiting and predicting IL-2 toxicity, and more recent trials using intermediate and low dosage regimens (rather than high dose protocols) have reported that patients tolerated the regimen and received the majority of scheduled doses. In addition, the increasing use of subcutaneous administration has significantly reduced the severity of adverse effects (Atzpodien & Kirchner 1991). With careful prescreening and patient education, IL-2 has been given in outpatient settings (Figlin et al. 1992; Flaherty et al. 1990; Hirsh et al. 1990; Kirchner et al. 1990; Mitchell et al. 1988; Ratain et al. 1993). Therefore, it appears that the adverse effects of IL-2 are dosage and schedule-dependent, with high dose, bolus adminstration having the highest toxicity, and low dose, subcutaneous administration incurring minimal adverse effects.

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Table VIII. Classification of toxicity according to Common Toxicity Criteria (after Gansbacher et al. 1992)

Grade	Definition
0	No toxicity
1	Mild toxicity, frequently of a transient nature, usually requiring no special treatment and generally not interfering with normal daily activities
2	Moderate toxicity, relieved by simple procedures
3	Severe toxicity, interrupting daily activity and requiring therapeutic intervention Hospitalisation may or may not be required
4	Life-threatening toxicity which requires hospitalisation

Most adverse effects appear to be due to a multisystem capillary leak syndrome, and current research is directed toward minimising this pathophysiology. Mortality rates of 1 to 6% have been noted (Dillman et al. 1991b; Rosenberg et al. 1989), with a lower incidence of morbidity and mortality in patients with a better performance status. In more recent trials, particularly in those using subcutaneous regimens, the incidence of treatment-related deaths has been $\leq$1.8% (Atzpodien 1992; Dillman et al. 1993). Typically, the return to pretreatment status is rapid after the cessation of IL-2 therapy, and patients are usually able to be discharged from hospital within 3 days. Adverse effects evinced by patients receiving IL-2 can be subdivided into effects on different organ systems. However, as most patients have $\geq$1 adverse effect occurring concurrently, holistic clinical evaluation is required. Recent trials tend to use the Common Toxicity Criteria (table VIII), which classifies the adverse events on a scale of 0 (no toxicity) to 4 (life-threatening). Several comprehensive reviews of the toxicity associated with IL-2 have been published (Margolin et al. 1989; Siegel & Puri 1991; Vial & Descotes 1992).

At present there is little evidence to suggest that combination therapy has a beneficial effect on adverse events associated with either IL-2 or the concomitant agent. In fact, toxicity may be additive: despite a good response rate, high dose regimens of IL-2 and IFN-α produced unacceptable adverse effects in two preliminary studies in patients with melanoma (Calabresi et al. 1991; De Mulder et al. 1991), and in a phase II trial in patients with renal cell carcinoma (Fosså et al. 1993). It has been suggested, however, that low dosage regimens of both agents produce the same response rates as high dose monotherapy, and therefore reduce toxicity without compromising efficacy (Lipton et al. 1993). Effects of low dose regimens or alternative methods of administration are discussed in section 4.

3.1 General Effects

Flu-like symptoms (e.g. fever, myalgia, fatigue) occur in >85% of IL-2 recipients but are usually mild, particularly in patients receiving subcutaneous regimens. Symptoms tend to appear a few hours after administration, thereby implying that they are not directly mediated by IL-2, but are due to IL-2-induced release of other cytokines, possibly IFN-γ or TNF-α. Two patients have developed acute arthritis *de novo*, and exacerbations of pre-existing arthritis with IL-2 have been reported (Scheibenbogen et al. 1993). Acute hypersensitivity reactions have not been described, but IL-2 treatment may predispose to reactions to iodinated and ionic contrast media (Choyke et al. 1992; Heinzer et al. 1992; Oldham et al. 1990; Shulman et al. 1993). Symptoms included vomiting, diarrhoea, malaise, fever and chills, skin rash or urticaria, facial oedema and sometimes itching, lethargy with hypotension, dyspnoea and acute renal failure. These occurred 2 to 4 hours after the injection of the contrast medium and resolved rapidly, but recurred with each injection. In most of these patients, previous administrations of iodinated contrast media had been well tolerated (Abi-Aad et al. 1991).

Attempts have been made to link adverse effects with parameters monitored for clinical response, or changes in other cytokine levels during IL-2 therapy. Clinical toxicity objectively measured by the degree of hypotension, tachycardia, fever and chills, correlated well with the levels of IFN-γ but not with TNF-α levels in 23 patients receiving IL-2 (Economou et al. 1991). However,

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in rats, passive immunisation against TNF effectively inhibited IL-2-induced hypotension, capillary leakage and the adherence of leucocytes to endothelium, but had no effect on tachycardia. This suggests that TNF mediates some, but not all, of the toxic effects of IL-2 (Edwards et al. 1992). Similarly, symptoms were reduced when patients received IL-2 with concomitant dexamethasone, a steroid that inhibits TNF release (Mier et al. 1990). However, dexamethasone is not recommended for control of adverse effects as it may reduce the efficacy of IL-2 (Anon. 1992a). Concomitant melatonin with IL-2 therapy considerably reduced the incidence of hypotension without influencing other adverse events (Lissoni et al. 1990). In addition, levels of soluble CD25 (the p55 subunit of the IL-2 receptor complex) have been correlated with hypotension, weight gain and decreased Karnofsky scores during IL-2 treatment, and were not significantly affected by the coadministration of LAK cells (Bogner et al. 1992). Other studies have indicated that the arachidonate cyclooxygenase pathway may be involved in the initiation of the host stress response to IL-2 therapy (Michie et al. 1988).

Adverse effects may be exacerbated if the presence of inadequate oxygen delivery due to the increased oxygen demand (caused by resuscitation measures) is not adequately managed (Silverman et al. 1988).

3.2 Cardiovascular and Pulmonary Effects

The capillary or vascular leak syndrome, now well documented with IL-2 therapy, is characterised by damage to endothelial cells, with extravasation of plasma proteins and fluid from capillaries into the extravascular space. Clinically, this syndrome manifests with hypotension, generalised non-pitting oedema, weight gain (often >10% of bodyweight), and other cardiopulmonary complications which include dyspnoea and pulmonary congestion. In addition, oliguria and raised serum creatinine levels occur as a consequence of poor central arterial pressure. As these changes are similar to those evinced in the early stages of septic shock (Diana & Sculier 1990; Ognibene et al. 1988; Wagstaff et al. 1989), care must be taken to ascertain the primary cause, as infectious complications are also common with IL-2 therapy (see section 3.10). As most manifestations of capillary leak syndrome resolve rapidly with cessation of therapy, withholding or delaying a dose may be the most effective means of determining the origin of the symptoms.

Manufacturer's data suggest that hypotension occurs in 85% of patients, and approximately 70% of patients will require vasopressor support with bolus administration of IL-2 (Anon. 1992a). Hypotension requiring vasopressor treatment was reported in 277 of 423 patients (65%) in one early study (Lee et al. 1989). Studies using low dosage subcutaneous IL-2 regimens report a reduction in severity but not usually in incidence of hypotensive episodes (Atzpodien & Kirchner 1991; Lissoni et al. 1992a; Whitehead et al. 1990). However, in 10 patients with 'excellent performance status' and no cardiopulmonary problems who received IL-2 3×10^6 IU/m^2/day by continuous infusion for 5 days, the only haemodynamic effect noted was tachycardia, suggesting that haemodynamic effects may be avoided by careful patient selection (Groeger et al. 1991).

The mechanism of capillary leak syndrome is uncertain. IL-2 has been shown to suppress the endothelin-1 secretion by endothelial cells, which may affect cell permeability and function (Taniguchi et al. 1992). Marked complement activation has been noted during and after IL-2 therapy, without the usual accompanying neutrophil activation (Moore et al. 1991; Wagstaff et al. 1989). T cells activated by IL-2 *in vitro* or *in vivo* bind complement, a reaction amplified by C-reactive protein induced by IL-2 (Vachino et al. 1991). As several complement products are known to increase vascular permeability, this may be responsible in part for the capillary leak syndrome observed with IL-2 therapy (Wagstaff et al. 1989). However, Baars et al. (1992c) observed raised levels of lactoferrin and elastase/α_1-antitrypsin, together with increased levels of complement C3a in patients receiving IL-2; thereby suggesting that activation of polymorphonuclear neutrophils may in some way initiate the capillary leak syndrome. It has been hypothesised that ac-

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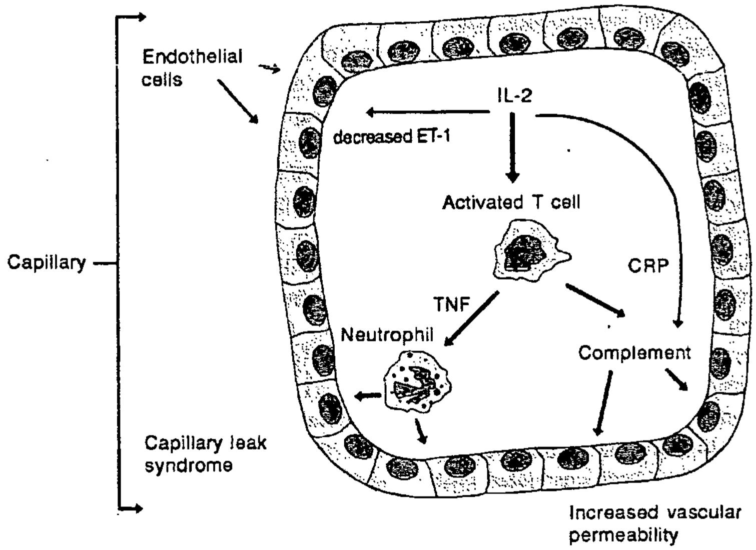

Fig. 4. A schematic representation of the probable interactions that result in capillary leak syndrome. *Abbreviations:* CRP = C-reactive protein; ET-1 = endothelin-1; IL-2 = interleukin-2; TNF = tumour necrosis factor.

tivation of neutrophils is possibly induced by TNF, given the time course of the cytokine profile, and passive immunisation against TNF partially abrogates the adverse effects (Baars et al. 1992c; fig. 4).

Myocardial toxicity may be a consequence of capillary leak syndrome as it has been reported in patients with or without underlying coronary artery disease (Kragel et al. 1990a,b; Nora et al. 1989; Ravaud et al. 1992). Significant increases in heart rate and cardiac output, a decrease in mean systolic arterial blood pressure to <100mg Hg, a drop in systemic vascular resistance and a reduction in cardiac contractility with depressed left ventricular ejection fraction have been found in most patients treated with high dosages of IL-2. Several cases of severe cardiomyopathy have been observed after IL-2 therapy, with symptoms appearing during the first few days of treatment, or several hours after the infusion was terminated (Goel et al. 1992). Angina and electrocardiographic changes indicative of ischaemia were noted in 2.6% of 317 patients, with documented myocardial infarction in 1.2% (Lee et al. 1989). Other investigators have found similar or higher incidences of these effects (Kragel et al. 1990b). Eosinophilic myocarditis may be a contributing cause of cardiac toxicity in some patients (Azar & Theriault 1991; Kragel et al. 1990a,b; Samlowski et al. 1989; Schuchter et al. 1990). In isolated rat hearts perfused with IL-2, no cardiotoxic effects were seen, indicating that toxic effects are unlikely to be due to direct action of IL-2 on heart muscle (Favalli et al. 1990), a finding supported by morphological data (Zhang et al. 1993).

Multiple types of arrhythmia have also been observed in patients receiving intermediate or high dose IL-2 therapy. Sinus bradycardia, atrial fibrillation, ventricular premature beats, and transient or sustained life-threatening ventricular tachycardia have been observed, with supraventricular tachyarrhythmias being the most clinically significant finding. There have also been isolated reports of atrioventricular block (Landonio et al. 1991).

Pulmonary congestion, interstitial oedema and dyspnoea are common results of capillary leak syn-

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drome, occurring in more than 50% of patients (Conant et al. 1989; Saxon et al. 1991). Up to 20% of these patients developed respiratory failure severe enough to warrant intubation. A larger study in 423 patients showed an incidence of severe respiratory distress of 9.2%, and 27 patients (6.4%) required intubation (Lee et al. 1989). IL-2 dosages in this trial ranged from 1.2 to 6 × 10^6 IU/kg 8-hourly. Pulmonary complications may be higher in patients receiving bolus administration of IL-2, and/or accompanying adoptive immunotherapy (Dillman et al. 1993; Villani et al. 1993).

The incidence of pleural effusions has been high in some studies (48% and 52% of patients; Saxon et al. 1991; Vogelzang et al. 1992) and low in others (1.9%; Lee et al. 1989).

3.3 Renal Effects

Acute renal failure, presumably due to the hypotensive effects of capillary leak syndrome, is one of the major complications of IL-2 therapy. Severe oliguria or anuria, and azotaemia with increased serum creatinine levels, occurs in >60% of patients. In addition, increased aldosterone and plasma renin activity, with low fractional sodium excretion have been observed. Generally, renal dysfunction is transient, and tends to resolve within 1 week of therapy cessation (Cochat et al. 1991). Baseline serum creatinine levels may indicate the level of renal insufficiency likely to be induced by IL-2, with pretreatment levels ≥15 mg/L indicating more severe dysfunction (Belldegrun et al. 1989). Transient proteinuria has been noted in a few patients with nephrotic syndrome receiving IL-2 (Bastuji-Garin et al. 1990; Hisanaga et al. 1990). However, proteinuria may be due to contaminants in the various IL-2 preparations, as results have been inconsistent (Heslan et al. 1991).

Direct intrarenal effects of IL-2 have been postulated, in addition to the extrarenal effects due to capillary leak syndrome (Chan et al. 1991; Feinfeld et al. 1991; Shalmi et al. 1990). Lithium clearance measurements showed significantly increased reabsorption of sodium and water, and reduced clearance of creatinine, sodium and lithium indicative of tubular dysfunction (Heys et al. 1993). Low dose dopamine infusion may mitigate these effects (Palmieri et al. 1993). Histological evidence of interstitial nephritis and glomerulonephritis has been observed in isolated case studies (Chan et al. 1991; Feinfeld et al. 1991).

3.4 Gastrointestinal Effects

Minor and reversible gastrointestinal adverse effects have been reported in over 80% of patients receiving IL-2 therapy (Margolin et al. 1989). Nausea and vomiting were easily treated with antiemetic agents. However, extreme diarrhoea (possibly resulting from bowel oedema) may warrant withholding IL-2 if electrolyte imbalance looks likely. Oral dryness with reduced saliva production and altered composition have been noted (Marmary et al. 1992).

Other less frequent gastrointestinal adverse effects are anorexia, peptic ulceration and stomatitis. Rarely, bowel haemorrhage, perforation, infarction and exacerbation of Crohn's disease have been reported (Rahman et al. 1991; Schwartzentruber et al. 1988; Sparano et al. 1991, 1993a). The use of concomitant IFN-α appears to increase the incidence of severe diarrhoea and bowel ischaemia (Sparano et al. 1991). A single case of pseudo-obstruction requiring decompressive colonoscopy has been reported (Post et al. 1991).

3.5 Hepatic and Metabolic Effects

Approximately 60% of patients undergoing IL-2 therapy develop asymptomatic abnormalities in liver enzymes, with transaminase levels increasing >5-fold. Raised bilirubin levels are common (up to 10-fold increases have been reported) but are typically transient, returning to within normal limits 5 or 6 days after therapy ceases (Huang et al. 1990). Remaining hepatic abnormalities tend to resolve within 1 month.

Hepatic changes are thought to be due to a profound cholestasis (Fisher et al. 1989), which has been noted to recur on rechallenge with IL-2 in one patient (Hoffman et al. 1989). In addition, hepa-

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tocellular toxicity may occur, suggested by a progressive hypoalbuminaemia that may not be entirely due to capillary extravasation. 4% of patients may be expected to develop ascites (Anon. 1992a).

Mean serum ascorbic acid levels have been observed to decrease rapidly to undetectable levels following the initial dose of IL-2 therapy, returning to normal within 1 month after therapy ceased (Marcus et al. 1991). Marked, reversible, recurrent decreases in high-density lipoproteins, low-density lipoproteins, and pretreatment hypercholesterolaemia have also been noted (Lissoni et al. 1991b).

3.6 Endocrine Effects

Numerous instances of IL-2-associated thyroid dysfunction have been reported, with symptoms usually developing within 2 months of starting treatment (Atkins et al. 1988; Besana et al. 1991; Berthaud et al. 1990; Hartmann et al. 1989; Jacobs et al. 1991; Kung et al. 1992; Lim et al. 1991a; Mattijssen et al. 1990; Pichert et al. 1990; Sauter et al. 1992; Scalzo et al. 1990; Schwartzentruber et al. 1991). Manufacturer's data suggest that the incidence is <1% of patients (Anon. 1992a); however, one study in 146 patients reported an incidence of hyperthyroidism of 14% (Viens et al. 1992), and another study reported thyroid dysfunction in 22% of 89 patients (Kruit et al. 1993). The severity of the symptoms vary, with some patients presenting with a marked decline in serum thyroxine, and others with clinical signs of hypothyroidism, hyperthyroidism and occasionally goitre (Mattijssen et al. 1990). The incidence may increase with multiple cycles of therapy, or with combination therapy with either LAK cells or IFN-α2. Patients receiving IL-2 and IFN-α therapy appear to develop hyperthyroidism by the second or third treatment cycle, followed by hypothyroidism which resolved within 6 months (Pichert et al. 1990). Most cases show an induction or exacerbation of autoimmune thyroid reactions, with development of autoantibodies. Thyroid dysfunction was correlated with treatment duration but not with clinical response in 89 patients (Kruit et al. 1993), whereas previous studies have postulated associations with clinical response in smaller groups of patients (Atkins et al. 1988; Reid et al. 1991).

Acute pancreatitis has also been described in isolated cases (Birchfield et al. 1990; Redman et al. 1990), but may be due entirely or in part to concomitant medications and patient history.

Adrenal haemorrhage leading to acute adrenal insufficiency has been observed in 1 patient who had pre-existing adrenal metastases (VanderMolen et al. 1989). Elevated levels of plasma cortisol, adrenocorticotropic hormone, and β-endorphin, adrenaline (epinephrine) and noradrenaline (norepinephrine) have also been observed during IL-2 therapy (section 1.3.4).

3.7 Haematological Effects

Anaemia occurs in 20 to 80% of IL-2 recipients, and frequently requires red blood cell transfusion. Lymphocyte counts initially decrease during therapy, but usually undergo rebound lymphocytosis after therapy ceases. Leucopenia is generally moderate, and is more frequently associated with lymphopenia rather than with severe neutropenia, which occurs less often. However, IL-2 therapy accelerated neutrophil recovery and myelopoiesis (perhaps via GM-CSF) after ablative chemoradiotherapy (Heslop et al. 1991a,b). These effects are possibly mediated by a cytokine-inducible, high-output L-arginine/nitric oxide pathway. The generation of nitric oxide may contribute to tumour regression, but could also be responsible for some of the adverse effects associated with IL-2 therapy (Hibbs et al. 1992). Eosinophilia occurs in most, if not all, patients with no clinical sign of hypersensitivity, and is possibly mediated by IL-5 (Macdonald et al. 1990a). Thrombocytopenia is a common adverse effect of IL-2 therapy (Guarini et al. 1991; Paciucci et al. 1990), with clinical manifestations of splenomegaly, splenic sequestration of autologous platelets, venous thrombosis and disproportionate bleeding, suggesting that IL-2 may induce both quantitative and qualitative platelet dysfunction (Fleischmann et al. 1991). Other haematological adverse effects include coagulation disorders (as the levels of most clotting factors de-

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cline) and more rarely, purpura and petechiae (Birchfield et al. 1992; Fleischmann et al. 1991; Richards et al. 1991). There have also been reports of activation of coagulation and fibrinolysis in patients receiving IL-2 (Baars et al. 1992a).

The mechanisms underlying the haematological adverse effects of IL-2 are difficult to determine, due to the complex interaction of many cytokines involved in the regulation of haematopoiesis. Peripheral eosinophilia is frequently accompanied by capillary leak syndrome, which may be mediated by major basic protein, a toxic eosinophil granule protein (van Haelst Pisani et al. 1991). Huland and Huland (1992) noted that while systemic eosinophils were increased by local IL-2 administration, the eosinophil population localised at the tumour site (in this case, in the urinary bladder) were both increased and actively releasing granule proteins. It has been suggested that thrombocytopenic effects are partly due to the autologous LAK cells induced by IL-2 administration (Guarini et al. 1991). Induction of thrombocytopenia appears to be mediated by mononuclear cells, possibly by increased production of thromboxane B_2 (Remick et al. 1987; Welbourn et al. 1990). Thromboxane B_2 is also implicated in the mechanism of IL-2-induced lung injury (Klausner et al. 1991; O'Neill et al. 1991) as is leukotriene B_4 (Klausner et al. 1990) and platelet activating factor (Rabinovici et al. 1992).

Inhibition of haematopoietic progenitor cells by IL-2 may be due to IL-2-induced cytokine production (in particular IFN-γ and TNF-α) rather than to the generation of LAK cells (Clerigue et al. 1990). However, *in vitro* studies in normal haematopoietic stem cells cultured with IL-2 and LAK cells, indicated that the inhibition of haematopoiesis was due to cellular mechanisms requiring cell-to-cell contact rather than released humoral factors (Schulze et al. 1992). The rapid resolution of the abnormalities at the cessation of IL-2 therapy indicates that liver dysfunction is unlikely to be involved.

Splenic enlargement has been reported in 5 of 9 patients receiving IL-2 by continuous infusion; there was no evidence to suggest this response was associated with the presence of metastases, rebound lymphocytosis or eosinophilia (Ratcliffe et al. 1992).

In summary, the haematological abnormalities evinced with IL-2 are likely to result from an imbalance of many interacting factors determining the clinical manifestations.

3.8 Neurological Effects

Neurological changes in patients undergoing IL-2 therapy vary from severe behavioural to moderate cognitive disturbance, with >70% of patients experiencing some change in mental status, although clinically relevant symptoms may be reduced with subcutaneous therapy. In a study in 61 patients receiving IL-2 subcutaneously, the incidence of neuropsychiatric symptoms was 23% (Buter et al. 1993a). Psychiatric adverse effects include paranoid delusions, hallucinations and somatic changes such as loss of interest, sleep disturbances or drowsiness, decreased energy, fatigue, anorexia and malaise (Denicoff et al. 1987; Fenner et al. 1993), symptoms similar to those observed in the acute phase of schizophrenia (Smith 1992). Coma, visual defects (Friedman et al. 1991), transient ischaemic attacks (Bernard et al. 1990; Donnet et al. 1991), paraesthesias (Fenner et al. 1993) and seizures have been observed. Increased latency and reduced amplitude in event-related evoked potentials have also been reported (Caraceni et al. 1993). Increased vascular brain permeability may be involved (Ellison et al. 1990), and preliminary studies using magnetic resonance imaging show increased cerebral water content of both grey and white matter in patients receiving IL-2 (Saris et al. 1989). Neurological adverse reactions may not resolve until several days after IL-2 therapy stops, and may actually worsen immediately following therapy cessation (Anon. 1992b). In addition, there is concern that the combination therapy of IL-2 with LAK cells may increase the possibility of subsequent brain metastases, by damaging the blood-brain barrier (Hayakawa 1992; Nakano 1992).

Few studies to date have explored the possibility of permanent neurological damage with IL-2

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therapy. Occasional axonal degeneration and demyelination has been observed in rat brain after IL-2 therapy (Ellison et al. 1990), possibly resulting from high levels of TNF activity (Ellison & Merchant 1991). In rats, parenteral injection of IL-2 caused increased permeability of the blood-brain barrier adjacent to tumour-bearing tissue, but effected no change on normal brain tissue (Alexander et al. 1989). Demyelination has also been noted on autopsy of a patient who developed neurological symptoms (vision disturbances, ataxia) and subsequently died after receiving IL-2 (Vecht et al. 1990).

Bilateral carpal tunnel syndrome has been reported in a single patient adminstered IL-2 therapy (Heys et al. 1992). Brachial plexopathy was demonstrated in two female patients receiving IL-2 therapy, with recurrence in one patient upon rechallenge (Loh et al. 1992).

3.9 Dermatological Effects

A variety of dermatological complications (mostly erythema and mucositis) have been reported, affecting almost all patients receiving high-dose IL-2, and >40% of patients receiving intermediate dosage regimens. In patients without underlying skin disease, erythema begins on the face and the neck 2 to 3 days after starting IL-2, with a more rapid onset observed if patients have also received LAK cells. Pruritus often accompanies the erythema, and can lead to dry desquamation lasting several weeks. The erythema generally resolves within 48 hours after cessation of therapy, and severity is dose-dependent in most instances, although some reports have suggested otherwise (Dummer et al. 1991). The presence of activated T helper lymphocytes in skin biopsies suggest that the skin is a target organ for immunotherapy (Dummer et al. 1991; Wolkenstein et al. 1993). Acute exacerbation of pre-existing psoriasis during high-dose treatment with IL-2 was observed in 3 patients.

Angioneurotic oedema and urticaria have been noted in smaller numbers of patients, with recurrence on rechallenge (Baars et al. 1992d). Life-threatening bullous skin lesions have also been observed in three patients (Staunton et al. 1991; Wiener et al. 1992), but did not recur on rechallenge, although erythema developed in one patient receiving a second course of therapy (Staunton et al. 1991). Subcutaneous administration of IL-2 caused transient inflammation at the injection site, and nodular lesions resembling subcutaneous lipomas, that gradually disappeared within 6 months (Sleijfer et al. 1992).

3.10 Infectious Complications

IL-2 therapy is accompanied by development of infection in approximately 23% of patients, with *Staphylococcus aureus* being the organism most commonly isolated (Lim et al. 1991b; Morère et al. 1993; Richards et al. 1991; Snydman et al. 1990). Sepsis is one of the major causes of death directly related to IL-2 therapy; however, as the use of prophylactic antibiotics for the placement of central intravenous catheters has increased, the incidence of infection and morbid sequelae has reduced markedly to approximately 7% (Pockaj et al. 1993). Subcutaneous administration of IL-2 may also limit the incidence of infection, although inflammation at the injection site is frequently observed (Kirchner et al. 1993; Sleijfer et al. 1992).

While the risk of infection is well recognised, due to the rise in body temperature induced by IL-2, an infectious response may be difficult to differentiate from a pharmacological response to the drug. Infections are correlated to some extent with the treatment regimen, with an increase in occurrence linked with the completion of the first cycle of therapy (Pockaj et al. 1993). Bacteraemia generally manifests approximately 3 weeks after the start of treatment, and is usually associated with the use of intravenous catheters (Orcese et al. 1990). Impairment of neutrophil chemotaxis persisting for up to 2 weeks after cessation of therapy has been reported, and may contribute to the development of infection (Klempner et al. 1990; Mier et al. 1990). Interestingly, severe neutropenia has not been associated with bacteraemia, whereas IL-2 concentration was significantly correlated with infection.

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Duration of intravenous therapy, concomitant LAK cell therapy, or underlying tumour type or source were not associated factors. A retrospective study in 519 patients showed that infected patients were more likely to be older, and that slightly more infected patients were female (Pockaj et al. 1993).

4. Dosage and Administration

Many different dosage regimens and administration methods have been used in clinical trials of IL-2. However, US labelling information states that IL-2 6×10^5 IU/kg should be administered as a 15-minute intravenous infusion every 8 hours for up to a total of 14 doses, with a further maximum of 14 doses after a variable rest period. A rest period of 9 days is suggested, but many clinical trials have used periods between repeat schedules of 3 days to several weeks. Doses are typically withheld rather than reduced in patients experiencing adverse events. In Europe, continuous infusion of IL-2 has been approved, the dosage usually being 18×10^6 IU/m^2/day for two 4.5- to 5-day cycles, with a rest period of about 6 to 8 days between cycles.

Some investigators have found no difference in overall response in patients receiving either continuous infusion or intravenous bolus regimens, although adverse events were reduced with continuous infusions (Clark et al. 1990; Dillman et al. 1993; Escudier et al. 1992). In contrast, some studies reported more severe adverse effects with continuous infusion compared to bolus administration (Fosså et al. 1993; Lopez et al. 1993), and less severe effects with subcutaneous regimens (Dutcher et al. 1993; Lissoni et al. 1992a, Sleijfer et al. 1992).

Subcutaneous IL-2 administration, although not yet approved, is frequently used in clinical practice. Generally, 18×10^6 IU is administered subcutaneously each day for 5 days, followed by a 2-day rest period. A dose of 9×10^6 IU is given on day 1 and 2 of the following week, followed by 18×10^6 IU daily for the next 3 days. Dosages are often reduced if IFN-α is administered concomitantly. Subcutaneously administered IL-2 appears to achieve similar response rates to continuous infusion or intravenous bolus regimens (tables V and VII). Escalating subcutaneous dosage regimens have achieved acceptable tolerability and similar clinical response rates compared with common intravenous dosage regimens in patients with cancer (Ratain et al. 1993; Schomburg et al. 1992). Patient gender, tumour type and cytotoxicity were not correlated with clinical response (Schomburg et al. 1992). Subcutaneous IL-2 20×10^6 IU/m^2/day for 3 days, followed by 5×10^6 IU/m^2/day 3 days per week for 5 weeks together with IFN-α 3 to 6×10^6 U/m^2 3 times weekly, resulted in objective responses in 33% of 80 evaluable patients with advanced renal cell carcinoma (Atzpodien 1992). These preliminary reports imply that subcutaneous regimens are well suited to home therapy, as this dosage regimen was well tolerated and effective.

Many other routes of administration have been used in IL-2 therapy, including slow delivery pellet (Fujiwara et al. 1991), extracorporeal perfusion (Belli et al. 1992), inhalation (Huland et al. 1992a,b) and regional injection. In many cases, a lower incidence of adverse events is reported with regional administration. Examples of regional administration are intratumoural, intravesicular (for bladder cancer; Cockett et al. 1991; Huland & Huland 1989), intrapleural (for malignant pleurisy; Lissoni et al. 1992b; Viallat et al. 1993) intrathecal (for brain metastases, usually from melanoma) endolymphatic (Galvani et al. 1992) intraperitoneal (Lissoni et al. 1992b; Melioli et al. 1991; Steis et al. 1990), intrapericardial (Lissoni et al. 1992b) and arterial perfusion of liver or spleen (Keilholz et al. 1992b; Klasa et al. 1990; Thatcher et al. 1989). The majority of these studies reported manageable toxicity, but overall clinical response was variable. Isolation perfusion using the extracorporeal circulation has shown promising results in a pilot study of 6 patients with recurrent metastases from cutaneous melanoma. Adverse effects were mild, and 5 of 6 patients showed objective responses (Belli et al. 1992). Inhaled IL-2 for pulmonary metastases has resulted in significant improvement in patient survival with few adverse effects, in a preliminary study in 15 patients (Huland et al. 1992a). Liposomes may be a promising future vector

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(Gause et al. 1993), as may be biodegradable microspheres (Hora et al. 1990). Further data are required before the comparative benefits of alternative means of administration can be identified.

Dosage schedules have also been the subject of much exploration. It appears that grade 3 and 4 toxicity may be avoided if patients receive low-dosage regimens of IL-2 (Caligiuri et al. 1991; Laghi Pasini et al. 1992; Stein et al. 1991). In addition, a non-linear dose response curve revealed by some clinical studies suggests that therapeutic responses are possible at dosages more than 10-fold below the maximum tolerated dose. Of overriding concern, however, is the possibility of reduced efficacy with lower dosages. Insufficient data exist to be sure that efficacy is not compromised when IL-2 is administered in low dosages; and although some small studies have been performed with similar response rates to those seen in trials using intermediate dosages, follow-up periods are too short to confirm response duration, and there have been no large prospective trials reported to date.

5. *Place in Therapy*

Most patients with metastatic malignancies have a poor prognosis, with the majority of patients included in studies of IL-2 having a 4- to 10-month survival. Consequently, although the clinical trials so far suggest that only about 1 patient in 5 will benefit from IL-2 therapy with a significant tumour response, this is an improvement over conventional therapy. In addition, responses are often more durable with IL-2 therapy. Thus, it is important to review the place of IL-2 therapy in the appropriate context.

Research into the pharmacodynamic aspects of IL-2 action indicates the breadth and complexity of interactions within the immune system and beyond, although further work is necessary before the role of IL-2 is fully characterised. The therapeutic use of IL-2 is even less well defined, and the possibilities for this agent are in the early stages of discovery. Table IX summarises the therapeutic outcomes and the total patient numbers studied to date, and it can be seen that IL-2 therapy, despite the large numbers of individual studies, remains in its infancy for most of the patient groups discussed in this review. The majority of studies have been performed in patients with renal cell carcinoma or malignant melanoma, where IL-2 appears to have a clear advantage over other therapeutic options, although well controlled comparative studies between different agents are lacking. Randomised studies that compared IL-2 as monotherapy or in combination with adoptive immunotherapy, IFN-α or chemotherapy have shown little difference between protocols.

In both renal cell carcinoma and in metastatic melanoma, IL-2 has a definite role in therapy. Objective response rates with IL-2 monotherapy in metastatic melanoma (13%) may be lower than those achieved in patients with renal cell carcinoma (20%) but combination therapy looks promising, unlike that for renal cell cancer treatment. Although complete responses are durable the partial response duration with IL-2 is somewhat disappointing, with relapses typically occurring after 6 months for patients with malignant melanoma, and in less than 10 months for patients with renal cell carcinoma.

In patients with colorectal cancer, results are inconclusive, but an objective response rate to IL-2 therapy of approximately 10% seems likely. Meta-analysis of randomised clinical trials comparing fluorouracil and fluorouracil plus calcium folinate therapy showed a response rate of 11% with fluorouracil and 23% with combination therapy, but no difference in survival (11 months) in patients with advanced colorectal cancer (Piedbois & Buyse 1993). Only one randomised trial has been conducted with fluorouracil plus calcium folinate with or without IL-2, but although response rate was 16%, the median survival was marginally higher (14 months) in patients receiving IL-2 (Eremin et al. 1993). Therefore, further studies are warranted to determine the comparative efficacy of IL-2 in the therapy of colorectal cancer.

Results in patients with ovarian cancer, bladder cancer or non-Hodgkin's lymphoma are inconclusive (table IX). The role of IL-2 is also undetermined in acute myeloid leukaemia, although it may

Table IX. Summary of the c

Type of cancer	Approx patients
Renal cell	>2000
Melanoma	>1800
Colorectal	>250
Ovarian	<50
Bladder	>50
Non-Hodgkin's lymphoma	>150
Acute myeloid leukaemia	>50

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Table IX. Summary of the clinical outcome of studies in patients with cancer receiving interleukin-2 (IL-2)

Type of cancer	Approx. no. of patients	Objective response rate	Range of objective response rate	Comments
Renal cell	>2000	20, 25%[a]	0-40%	Uncertain survival advantage with no objective response, no clear advantage with combined cellular therapy, or with other agents. Role of surgery inconclusive, but can convert partial to complete responses
Melanoma	>1800	13, 36%[a]	3-60%	Little survival advantage with no objective response, possible survival advantage with combined cellular therapy, and some advantage with combination therapy with >2 agents
Colorectal	>250	Inconclusive	0-42%	Trials too small for conclusions, however overall response rate may approximate 10%. Probable advantage with combination therapy, and IL-2 may be useful perioperatively
Ovarian	<50	Inconclusive	0-10%	Intraperitoneal administration may be useful in reducing drainage of peritoneal ascites, but no conclusive data available
Bladder	>50	Inconclusive	0->80%	Intravesical therapy with IL-2 and bacillus Calmette-Guerin promising
Non-Hodgkin's lymphoma	>150	Inconclusive	0-60%	Conflicting responses in different types of lymphoma, but aggressive disease may be more responsive. Possible advantage with cellular therapy, but evidence inconclusive. Patients may respond to retreatment after relapse
Acute myeloid leukaemia	>50	Inconclusive	Inconclusive	Response correlated with ≤20% leukaemic marrow blast cells. Possible role in maintenance/consolidation therapy

a Values are the average objective response rate in monotherapy, and combination therapy, respectively.

be useful as maintenance or consolidation therapy in improving the durability of remission. Nevertheless, in general, the available alternative therapies do not appear to be more effective, although comparative data are limited. IL-2 may be a useful adjunct to conventional therapy while its precise role is under investigation.

For the individual with metastatic disease, who has a likely remaining lifespan of less than one year, the primary concerns may be informed therapeutic choice and quality of life. In this context, the tolerability of IL-2 is likely to be an important factor. Systemic IL-2 therapy is associated with a range of severe adverse effects, particularly with high-dosages, and although most effects are rapidly reversible with cessation of therapy and can be reduced by lower dosage regimens, the potential for a fatal outcome remains. With this in mind, patient selection is vital, and guidelines have been formulated for the patients best suited to IL-2 therapy. These include:

- Clearly evaluable sites of disease refractory to other therapeutic measures
- Normal renal, pulmonary and hepatic function

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• Normal results on stress electrocardiography or thallium studies

• No known or suspected infections

• No antitumour therapy for 1 month prior to commencing IL-2 therapy

• No evidence of bleeding sites or abnormalities

• ECOG status of 0 or 1, or Karnofsky performance status of ≥80%, with estimated survival of ≥3 months

• No evidence of cerebral metastases within 1 month prior to commencing therapy (by computerised tomography)

• No requirement for immunosuppressive agents (e.g. steroids)

• No contraindication to the use of vasopressors (Anon. 1992b; Richards & Lotze 1992).

Symptom assessment forms that may improve patient management during IL-2 treatment have been developed for use in these patients (White 1992).

Combination therapies that maintain or improve efficacy while reducing the severity of adverse effects are also an option. This may be the main advantage in using IL-2 and IFN-α (Wersäll 1993), although one crossover study has shown little difference in either biological, clinical or adverse effects compared to IL-2 monotherapy (Schiller et al. 1993).

When considering toxicity issues, it must also be remembered that few alternative therapies are without adverse effects, and while these may not be as clinically severe as those associated with IL-2, they may be as distressing to the patient (e.g. alopecia with chemotherapy) in terms of quality of life.

Guidelines for selecting the patients most likely to respond clinically to IL-2 are less straightforward. Maldazys and deKernion (1986) reviewed 181 patients with metastatic renal cell carcinoma, and determined that survival for the entire group was 73% at 6 months, 48% at 1 year and 9% at 5 years. Improved survival correlated with a long disease-free interval between removal of the primary tumour and the discovery of metastases, metastases limited to the lung, and a normal performance status. In patients with acute myeloid leukaemia, it seems that those with low-grade disease may respond more frequently than those with aggressive disease. In contrast, patients with aggressive non-Hodgkin's lymphoma may be more suitable candidates for IL-2 than patients with less severe pathology. Clearly, IL-2 therapy will require selection and perhaps modifications in dosage and administration for patients with different neoplasms and various stages of disease. Furthermore, the pharmacodynamic data suggests that antigenic influences are possible, with both the type of tumour antigen and the patient haplotype perhaps determining clinical outcome. Thus, at present, there are many interesting avenues for further clinical research with IL-2, but few clear indications which is the most likely to be successful.

IL-2 therapy is therefore moderately effective in patients with metastatic cancer, but its use is limited by toxicity or poor targeting. Local adminstration, where applicable, deserves further exploration, as does liposomal encapsulation of IL-2. Future research in transgenic techniques may eventually enable the insertion of the IL-2 gene into tumour cells, which would direct the immunogenic effects to a precise location, and perhaps eliminate the systemic adverse events experienced with IL-2 therapy (Bubeník et al. 1993; reviewed in Foa et al. 1992a). Studies of immunisation with allogeneic altered melanoma cells that secrete IL-2 have been proposed in patients with metastatic melanoma (Gansbacher et al. 1992; Osanto et al. 1993). Encouraging results have been reported from a phase I trial performed with subcutaneous IL-2 in combination with murine monoclonal antibody targeted to a tumour cell antigen (Ziegler et al. 1992). Another possibility is that PEG-IL-2 may, by virtue of a longer half-life, enable reduced dosages and therefore decrease toxicity. Preliminary studies indicate this mode of treatment warrants further investigation (Katre 1990; Mattijssen et al. 1993; Meyers et al. 1991; Teppler et al. 1993a,b).

In summary, the role of IL-2 therapy in cancer therapy is promising but is as yet ill-defined, despite the substantial amount of research reported. The most convincing evidence supporting its use is found in the treatment of patients with meta-

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nount of research reported.
vidence supporting its use
ent of patients with metastatic renal cell carcinoma and melanoma, where IL-2 therapy has a greater likelihood of clinical response and longer survival duration than other currently available therapeutic options. Nevertheless, more studies are required to establish optimum dosage regimens for these patients, and toxicity remains a considerable problem with intravenously administered IL-2. For patients with colorectal, ovarian or bladder cancer, non-Hodgkin's lymphoma or acute myeloid leukaemia, IL-2 offers an adjunct to current therapy with the possibility of real therapeutic benefit but with firm evidence still required.

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17783662 PMID: 17387299
Diseases of large granular lymphocytes.
Alekshun Todd J; Sokol Lubomir
Malignant Hematology Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612, USA.
Cancer control - journal of the Moffitt Cancer Center (United States)
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BACKGROUND: Clonal diseases of large granular lymphocytes (LGLs) are rare lymphoproliferative malignancies that arise from either mature T-cell (CD3+) or natural killer (NK)-cell (CD3-) lineages. They manifest a distinct biologic behavior that ranges from indolent to very aggressive. METHODS: We discuss four distinct diseases involving LGLs: indolent T-cell LGL leukemia, aggressive T-cell LGL leukemia, chronic NK-cell ***leukemia*** , and aggressive NK-cell ***leukemia*** . Furthermore, we present an up-to-date systematic review of therapies for each entity. RESULTS: Sustained LGLs, characteristic immunophenotype, clonal origin of leukemic cells, and clinical presentation are the most important features that distinguish indolent from aggressive subtypes of LGL leukemia and guide the selection of therapy. Patients with symptomatic indolent T-cell or NK-cell LGL leukemia are usually treated with immunosuppressive therapies in contrast to aggressive T-cell and NK-cell LGL leukemia , which require intensive chemotherapy induction regimens. Novel targeted therapies using monoclonal ***antibodies*** against receptors, including CD2, CD52, the beta subunit of the interleukin-2 receptor, and small molecules such as tipifarnib, are undergoing evaluation in clinical trials. CONCLUSIONS: Future scientific advances focusing on the delineation of molecular pathogenic mechanisms and the development of new targeted therapies for each distinct LGL leukemia entity should lead to improved outcomes of patients with these disorders.

... to very aggressive. METHODS: We discuss four distinct diseases involving LGLs: indolent T-cell LGL leukemia, aggressive T-cell LGL leukemia, chronic NK-cell leukemia, and aggressive NK-cell ***leukemia*** . Furthermore, we present an up-to-date systematic review of therapies for each entity. RESULTS...

... clinical presentation are the most important features that distinguish indolent from aggressive subtypes of LGL leukemia and guide the selection of therapy. Patients with symptomatic indolent T-cell or NK-cell LGL leukemia are usually treated with immunosuppressive therapies in contrast to aggressive T-cell and NK-cell LGL leukemia, which require intensive chemotherapy induction regimens. Novel targeted therapies using monoclonal antibodies against receptors, including CD2, CD52, the beta subunit of the interleukin-2 receptor, and small molecules such as tipifarnib, are undergoing evaluation in clinical trials. CONCLUSIONS: Future...

... of molecular pathogenic mechanisms and the development of new targeted therapies for each distinct LGL leukemia entity should lead to improved outcomes of patients with these disorders.

Descriptors: *Antigens, CD3; *Killer Cells, Natural--pathology--PA; * Leukemia, Lymphoid--pathology--PA; *Leukemia, T-Cell--pathology --PA; *Lymphocytes--pathology--PA; Humans; Leukemia, T-Cell--drug therapy--DT; Leukemia, T-Cell--epidemiolog

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08565661    PMID: 3118104
   Malignant chronic lymphocytic leukemia B cells express
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interleukin 2 receptors but fail to respond to ***interleukin*** ***2*** 's proliferative signal.
Perri R T; Kay N E
Department of Medicine, Veterans Administration Medical Center, Minneapolis, Minnesota.
Leukemia - official journal of the Leukemia Society of America, Leukemia Research Fund, U.K (UNITED STATES) Feb ***1987*** , 1 (2) p127-30, ISSN 0887-6924--Print Journal Code: 8704895
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Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The functional importance of interleukin 2 (IL-2) receptors in the regulation of malignant B cell